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OF
OPHTHALMOLOGY

THIRD SERIES FOUNDED BY EDWARD JACKSON

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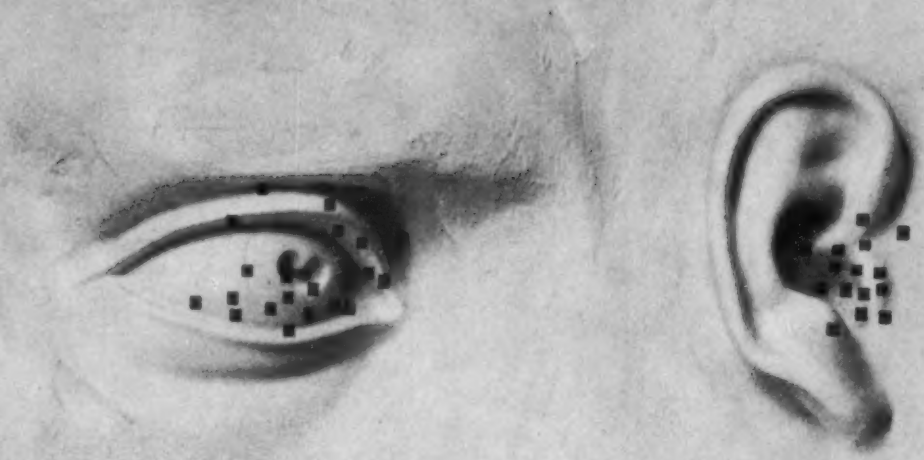
IF INFECTION IS PRESENT OR PROBABLE



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*Baer, R. L., and Witten, V. H.: Editorial Comment. *In* The Year Book of Dermatology and Syphilology (1958-1959 Year Book Series), Edited by Rudolph L. Baer and Victor H. Witten, Chicago, The Year Book Publishers, 1959, p. 40.

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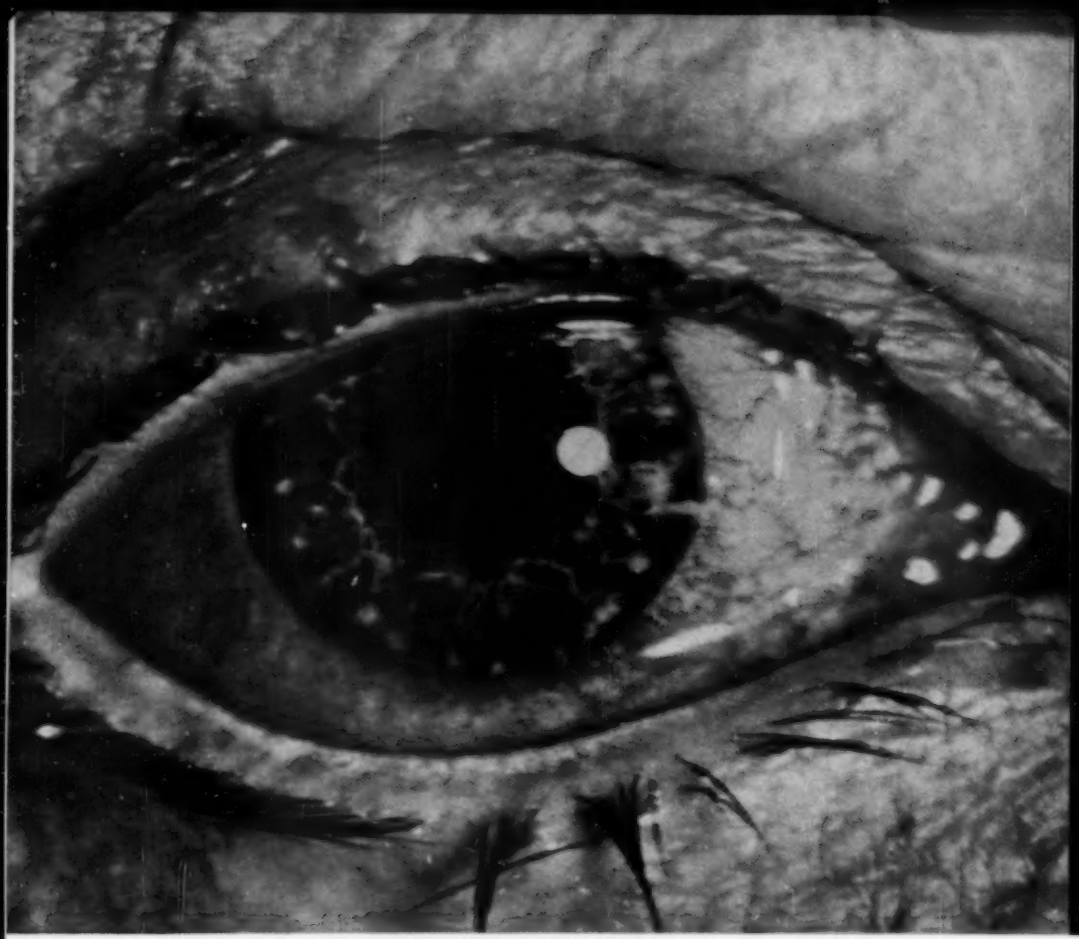

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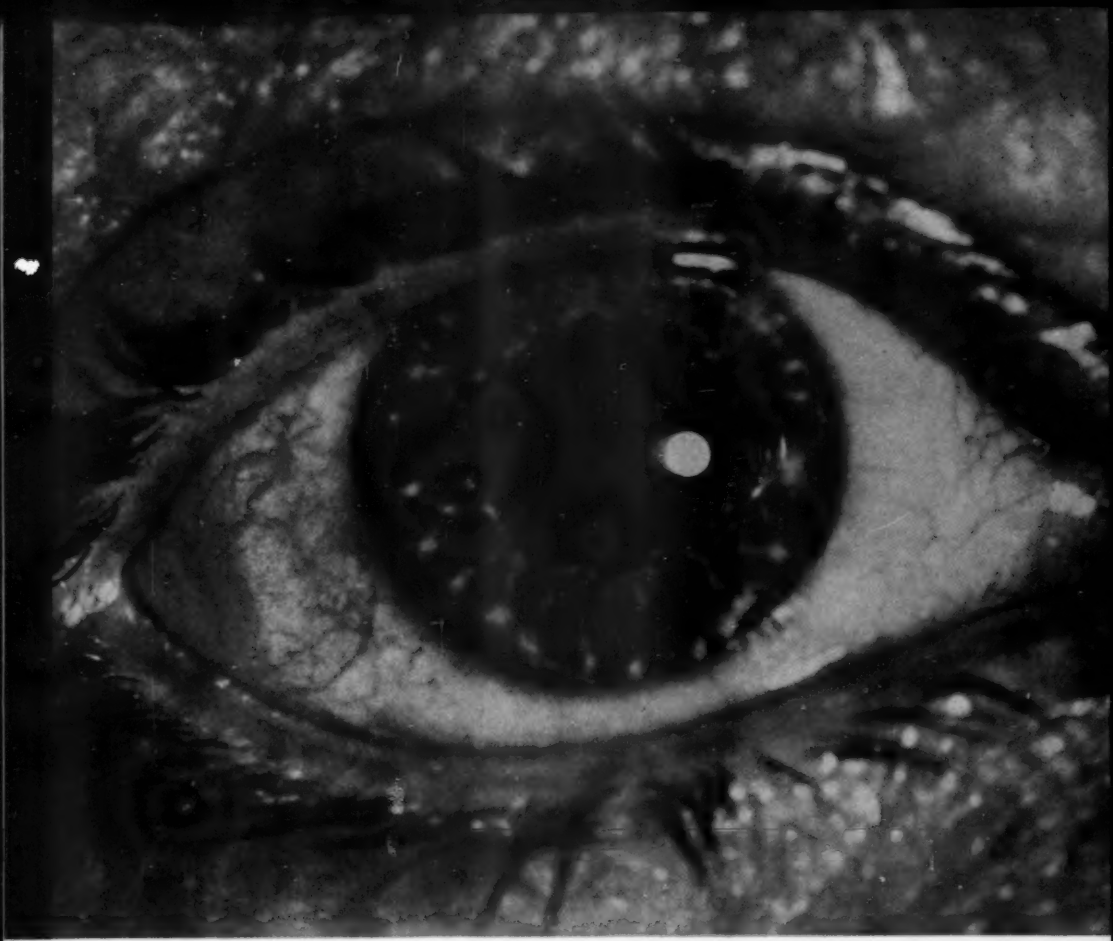
1. Gordon, D. M.: Scientific Exhibit, American Medical Association, Annual Meeting, San Francisco, 1958.



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NeoDECADRON Ophthalmic Ointment	0.05%	0.5 mg./Gm.	5 mg./Gm. (equivalent to 3.5 mg. neomycin base)	3.5 Gm. (⅛ oz.) tubes
DECADRON Phosphate Ophthalmic Ointment	0.05%	0.5 mg./Gm.	—	3.5 Gm. (⅛ oz.) tubes

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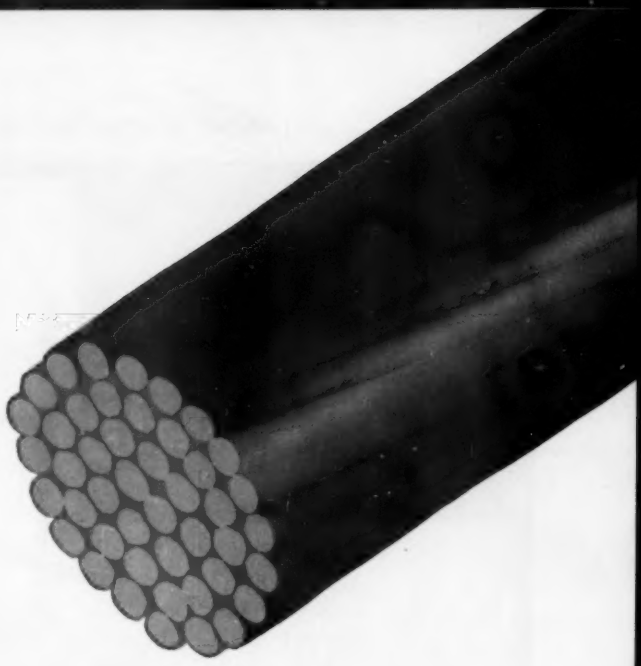

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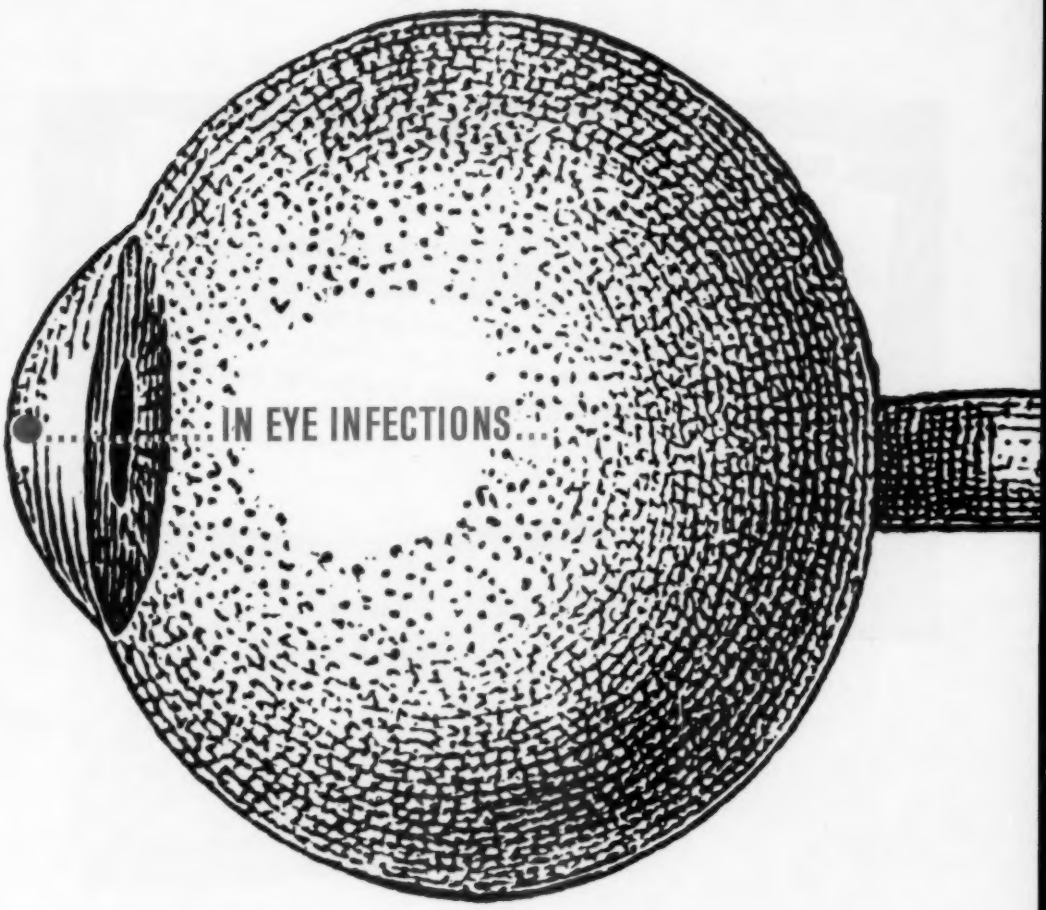

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PARKE-DAVIS

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alpha chymotrypsin

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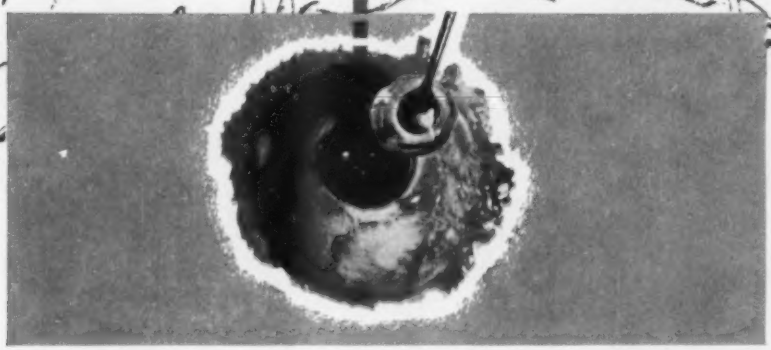

ALPHA CHYMAR—lyophilized crystallized chymotrypsin—loosens the zonule fibers of the lens within minutes, and thus "can serve to relieve that moment of anxiety for the cataract surgeon when he meets up with a tough zonula. [ALPHA CHYMAR] helped to prevent the complications of capsule rupture and of undue zonular traction on structures of the inner eye."[1]

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1. Thorpe, H. E.: Am. J. Ophth. *49*:531-547 (Mar.) 1960. 2. Schwartz, B., *et al.*: Tr. Am. Acad. Ophth. & Otol. *64*:46-54 (Jan.-Feb.) 1960. 3. Cogan, J. E. H.: Proc. Roy. Soc. Med. *51*:927, 1958. 4. Jenkins, B. H.: J.M.A. Georgia *45*:431, 1956. 5. Raiford, M. B.: J.M.A. Georgia *48*:163, 1959. 6. Rizzuti, A. B.: Arch. Ophth. *61*:135, 1959.

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TECHNIQUE OF APPLICATION:
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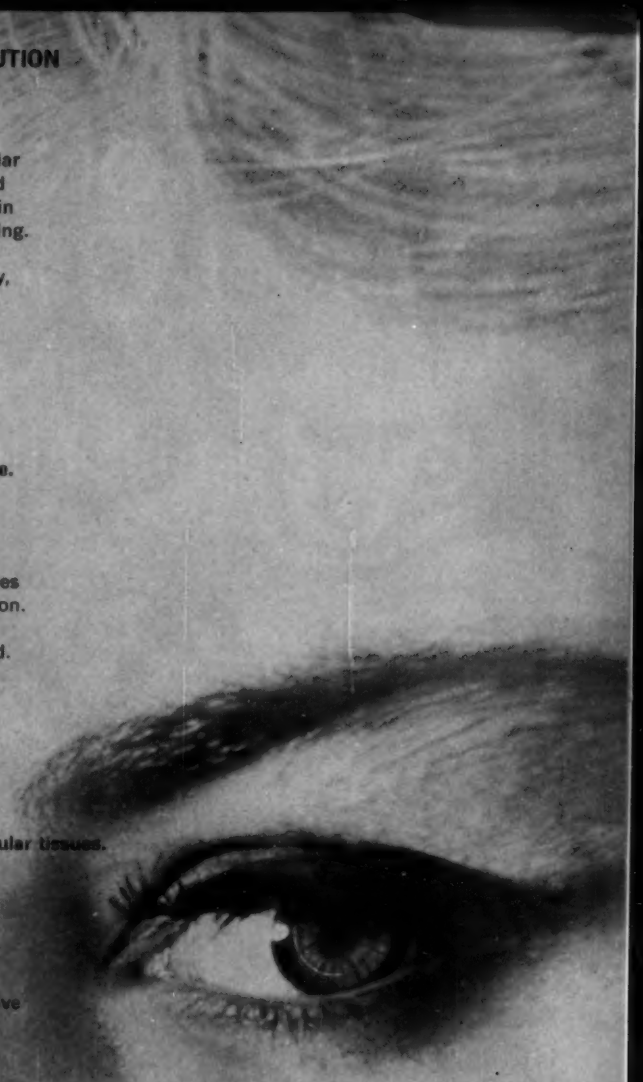
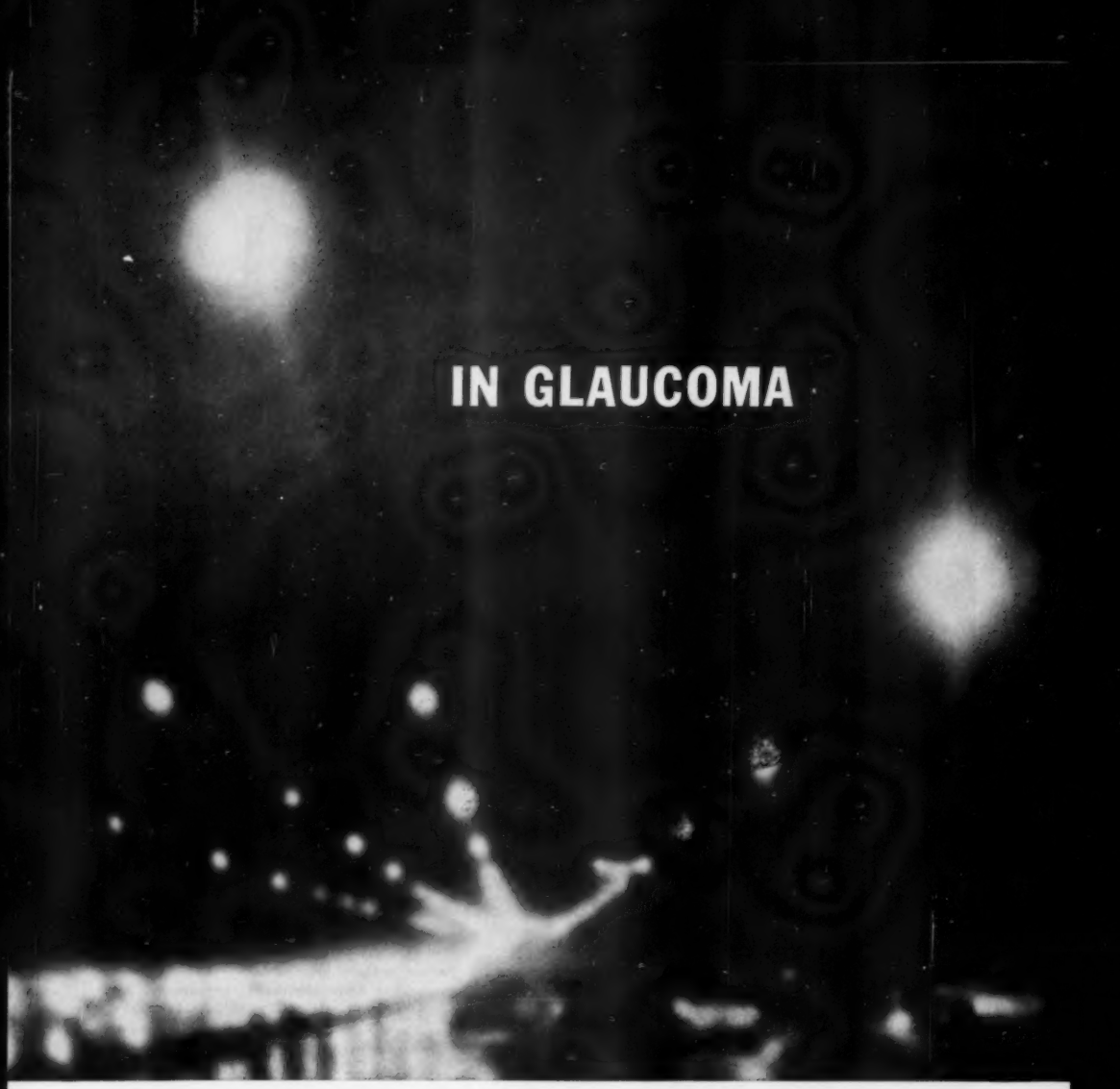


EFFECTIVE AIDS

to successful contact lens fitting/wearing

[1] CLIFTON, C. E. AND HALL, M. C. "RE-STERILIZING ACTIVITY OF CERTAIN CONTACT LENS SOLUTIONS." CONTACTS, THE CONTACT LENS JOURNAL, 3:10, 201-2, 1959.

Manufactured by **BARNES-HIND** OPHTHALMIC PRODUCTS, INC., 895 KIFER ROAD, SUNNYVALE, CALIFORNIA. REGENT 6-5462



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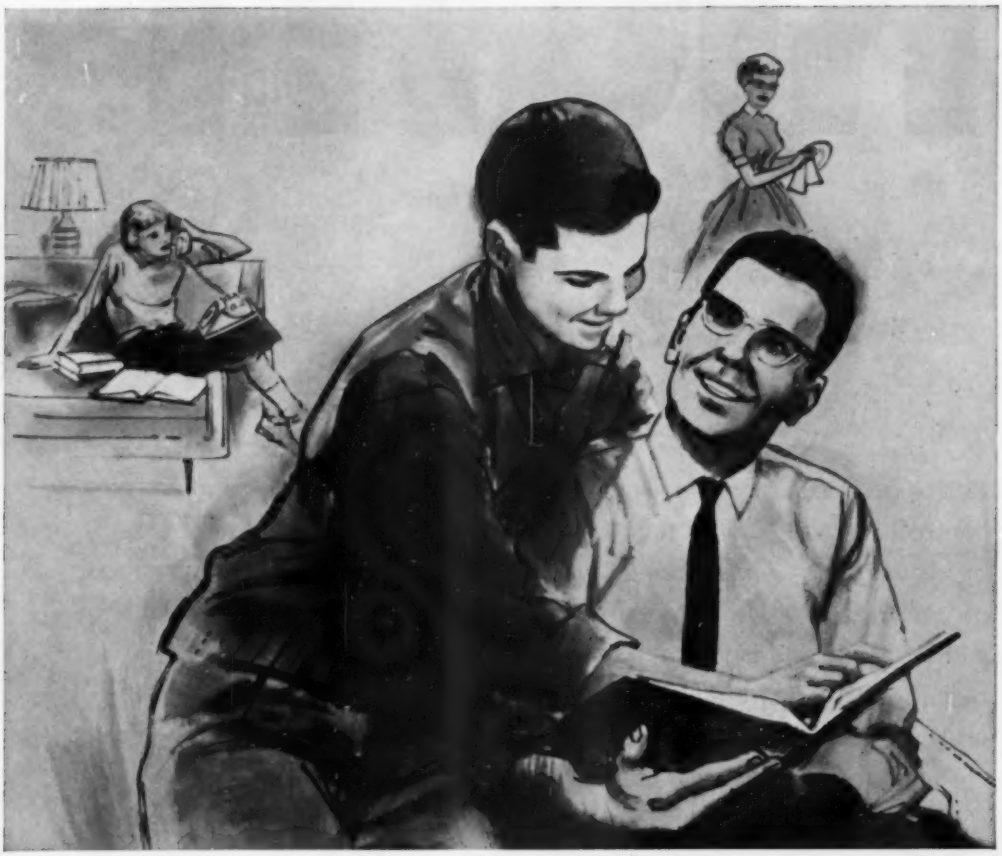
shape for "natural vision"



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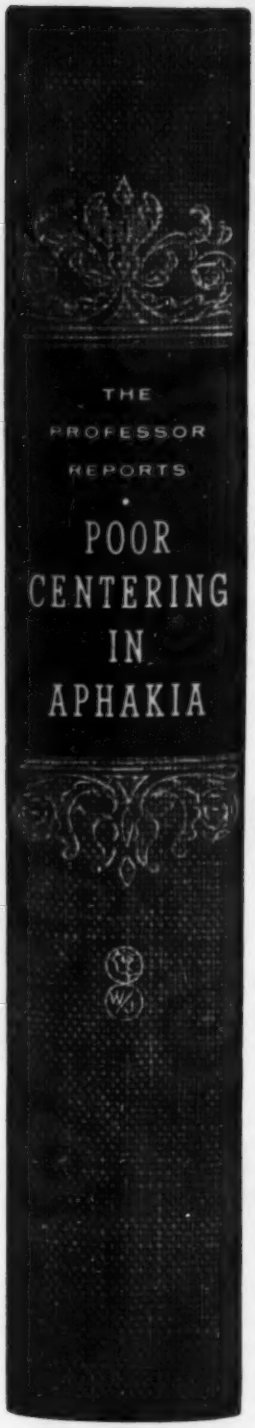

Very often problems will arise in the contact lens field which the individual practitioner has a difficult time solving. For example, let's discuss the aphakic patient who recently came to the attention of the The Plastic Contact Lens Company. The practitioner doing the fitting was having a difficult time getting adequate acuity through the contact lenses due to a problem of poor centering of the lenses on the eye. Regardless of the changes which the doctor requested on the lenses, the lenses constantly seemed to ride in a downward position in relation to the pupil of the eye. When the lenses were placed in a centered position, the acuity was excellent. When the lenses were allowed to drop to their downward position, the acuity was poor. The problem was to place the optical section of the lenses in such a position that it remained centered on the eye even though the lenses dropped downward.

The Plastic Contact Lens Company made a pair of lenticular lenses with a decentered optical portion. The manner in which the lenses were made placed additional weight on one side of the lens so that there was no rotation of the lens on the eye. With the optical portion of the lens riding toward the top of the lens, the patient's line of fixation was now directly through the optical portion and the acuity was good even though the lenses were still in a downward position.

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No other lens can give your patients as much *security*, comfort and satisfaction as AOLITE . . . the lens for active people of all ages. In addition to the advantages enumerated above, AOLITE is extremely effective in filtering out ultraviolet rays and has less tendency to fog or steam up. And . . . it employs the Tillyer Principle for accurate marginal vision. Available through your local AO Branch or AO Franchised Distributor.

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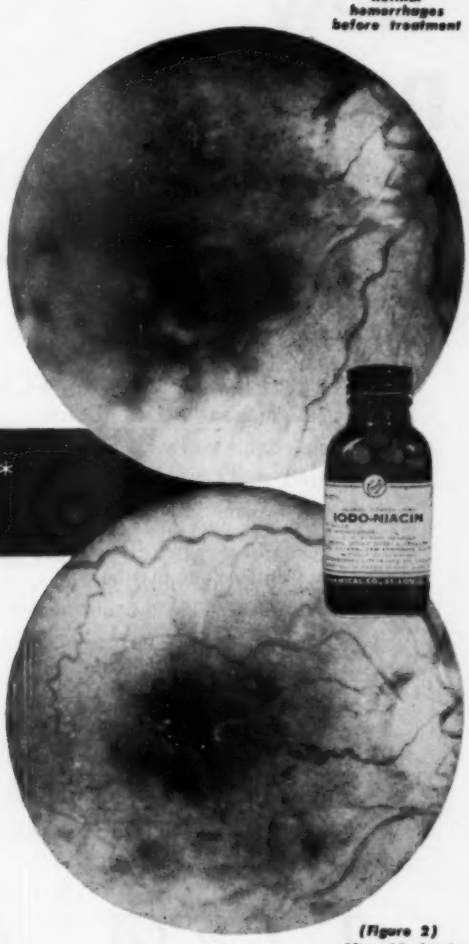
retinal hemorrhages absorbed

with use of

IODO-NIACIN*

(Figure 1)
Retinal hemorrhages before treatment



(Figure 2)
After 18 days' treatment with Iodo-Niacin

NO IODISM

As shown by retinal photography, rapid absorption of retinal hemorrhages follows use of IODO-NIACIN. These results have been established in a series of 22 cases, 12 of retinal and 10 of vitreous hemorrhages.[1]

IODO-NIACIN Tablets contain potassium iodide 135 mg. (2¼ gr.) and niacinamide hydroiodide 25 mg. (⅜ gr.). The dosage used was 1 tablet three times a day. For greater effect this dosage may be doubled.

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In emergencies, for rapid and intensive action, IODO NIACIN Ampuls may be used intramuscularly or intravenously.[3] IODO-NIACIN Tablets are supplied in bottles of 100. Slosol coated pink. Ampuls 5 cc. boxes of 10.

Cole CHEMICAL COMPANY
3721-27 Laclede Ave., St. Louis 8, Mo.

1. *Am. J. Ophth.* 42:771, 1956.
2. *Am. J. Digest Dis.* 22:5, 1955.
3. *Med. Times* 84:741, 1956.

*U.S. Patent Pending

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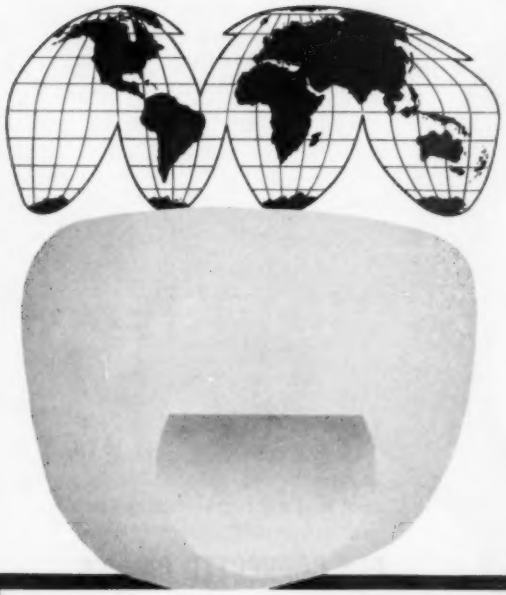

VISION-EASE

THE VISION-EASE CORPORATION
St. Cloud, Minnesota

VISION-EASE D-20 VISION-EASE D-22 VISION-EASE D-25 VISION-EASE D-28 VISION-EASE CEN-COR

The widest possible range of D-style bifocals, from the 20mm through the Cen-Cor, a decentered 28mm segment for the correction of horizontal prism correction in the reading area. Stocked in most-wanted forms in all Vision-Ease Branch Stock Offices . . . or, check your laboratory.

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"WIDESITE" is the word . . .

"WIDESITE"

FOR A BROAD LINE

The Widesite Line now includes two new base curves, 11.50 and 12.50; the large 60x62 blank in a greater range of powers; two new lenses, Dress Safety for heat treating, and Neutrex—neutral gray; a wider range in finished and semi-finished Greentex No. 3.

FOR MAXIMUM SIZE

Widesite Lenses are made in three sizes; 60x62, providing maximum glass area in low power prescriptions; a new *intermediate size* 56x58; and 52x54 for minimum thickness in high powers.

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"WIDESITE"

"WIDESITE"

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Each lens is checked with a grid on a screen for focus accuracy, and the optical center marked mechanically while the lens is in correct focus. Tolerances are ±0.06 diopters for meridional powers plano through 6.00 diopters, and ±0.09 diopters for meridional powers 6.25 through 10.00 diopters.

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SHURON OPTICAL CO., Rochester, N.Y.

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BIFOCAL TROUBLES

How many times have the legitimate complaints of a new bifocal wearer been brushed aside by the optician—forcing the patient to take his problems to the ophthalmologist, who will, in many cases, have to find the optician's mistakes. The following is a list of the most common mechanical defects of bifocal lenses which we believe will aid the ophthalmologist in finding the source of his patient's complaints.

1. Check the DISTANCE CENTERS to be sure they coincide with the patient's distance PD horizontally and *vertically*.
2. Examine the patient's eyes for both VERTICAL and HORIZONTAL ASYMMETRY and ascertain that any difference is incorporated in the position of the bifocal.
3. Hyperopes must have ADDITIONAL DECENTRATION of the bifocal segment to compensate for the base out prism created by the distance portion of the lens.
4. Incorrect BIFOCAL HEIGHT is probably the most common problem of bifocal wearers. Segments cause trouble when fitted either too high or too low for visual requirements. Because of prismatic effect, myopes tend to wear their bifocal higher and hold their reading material lower than hyperopes, although a myope is more likely to notice and therefore complain about a segment which intrudes on his distance field.
5. Induced VERTICAL IMBALANCE found at the reading point must be corrected if it exceeds one prism diopter. This can be achieved by the use of slab-offs, dissimilar segments or prism segments.
6. Glasses should be ADJUSTED so that they are horizontal with and equidistant from the eyes. They should be fitted close to the eyes in order to increase the angular field of the bifocal and make the division line less noticeable to the patient. Pantoscopic tilt (on all but heavy myopic prescriptions) helps bring the division line under and away from the patient's distance field.

All of these "bifocal troubles" are discussed individually in other Scientific Corner articles. Copies are available upon request.

AMERICAN JOURNAL OF OPHTHALMOLOGY

SERIES 3 · VOLUME 50 · NUMBER 2 · AUGUST, 1960

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AMERICAN JOURNAL OF OPHTHALMOLOGY

VOLUME 50 AUGUST, 1960 NUMBER 2

ELASTIC TISSUE DEGENERATION IN SICKLE-CELL DISEASE*

WALTER J. GEERAETS, M.D., AND DUPONT GUERRY, III, M.D.
Richmond, Virginia

In a recent study reported by us, degenerative changes in elastic tissue were found to occur in the eyes of patients with sickle-cell disease. Such changes were similar to those observed in angioid streaks of the ocular fundus in the Groenblad-Strandberg syndrome, although histologic differences were found. In one patient the triad of angioid streaks, pseudoxanthoma elasticum and sickle-cell disease was noted.

It was suggested that there might be a causal relationship between sickle-cell disease and elastic tissue pathology and that the ocular findings were either part of the generalized process, or perhaps secondary to the sickle-cell retinopathy.

The relatively high percentage (six percent) of angioid streaks noted in a large series of sickle-cell cases was thought to be more than coincidental and the changes noted were seen in patients with both hemoglobin S-S as well as in patients exhibiting the S-C type disease. In the cases reported of angioid streaks varying degrees of sickle-cell retinopathy were found.

Histologic examination of enucleated eyes from sickle-cell patients showed, in addition to the pathology in Bruch's membrane, definite defects in the lamina elastica interna of several long ciliary arteries and in one choroidal artery. The characteristic pathology noted in the lamina elastica was thickening, doubling, discontinuity over different wide areas and a featherlike spreading of elastic fibers at the edges of the lamina.

Since that time histopathologic studies have been carried out on all tissues of 16 sickle-cell autopsy cases. Tissues from healthy subjects who had died from accidents were examined as controls. In two of the sickle-cell cases, elastic tissue degeneration was found in arterial walls, while in the remaining cases and controls no such changes were seen.

Before discussing details of these pathologic findings, a review of the general systemic diseases in which elastic tissue pathology of the vascular system as well as of the ocular fundus occurs, seems justified. Because of the great similarity in the behavior of the elastic tissue in sickle-cell disease and Groenblad-Strandberg syndrome, the clinical and pathologic findings of the vascular system in the latter syndrome are considered first.

GROENBLAD-STRANDBERG SYNDROME

Involvement of the arterial system in pseudoxanthoma elasticum is today well known. Plang (1891) first described the existence of a shallow radial pulse in a patient with angioid streaks. The author explained this phenomenon as being due to decreased elasticity of the arterial wall. de-Schweinitz (1895) and Holloway (1927) then reported the frequent finding of clinical involvement of the arterial system in patients with angioid streaks. Oscillometric studies were first described by Ehlers and Marthinsen (1934) on a 48-year-old patient.

Prick (1938) reported the degeneration of elastic fibers in renal, mesenteric and coronary arteries in cases with associated angioid streaks. Urbach described in the same year

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degeneration of elastic tissue in brain arteries, in the media of the aorta, and in the brachial arteries of a 44-year-old male patient. Kat and Prick (1940) found degenerated elastic tissue fibers in the wall of the larger arteries of a surgically removed thyroid gland of a patient with pseudoxanthoma elasticum.

Balzer (1884) described degeneration involving elastic elements in the walls of the pulmonary alveoli and Kat and Prick (1940), degeneration of elastic fibers in mesenteric, pancreatic, renal, uterine, coronary and cutaneous arteries, hepatic veins, splenic trabeculae and Bruch's membrane.

Urbach and Wolfram (1938) reported on histologic changes in the aorta, cerebral, brachial, and cutaneous arteries, as well as in Bruch's membrane, while Scheie and Freeman (1946) found elastic tissue degeneration in a biopsied ulnar artery, showing compensatory muscular atrophy. Degeneration of the lamina elastica interna of vessels in the gastric wall, in addition to microaneurysms, was present in a 23-year-old white woman (Kaplan and Hartman, 1954), but usually the tunica elastica interna of the vessels remained intact. The arterial changes, which were often advanced, were at times difficult to distinguish from ordinary atherosclerosis and arteriolosclerosis.

The reduction or loss of arterial pulsation in the limbs was considered by Carlberg to result from degeneration and fragmentation of elastic tissue in the vessel wall and not to occlusion of the vessel lumen. Pronounced calcification in the peripheral arteries occurring secondarily in areas of degenerated elastic tissue, was described also in affected areas of the skin (Finnerud and Nomland, 1937) and degeneration of elastic tissue and calcification was found in intestinal vessels by Prick (1938) and Hagedoorn (1939) where there had been a terminal gastro-intestinal hemorrhage.

Bäfverstedt and Lund (1954) pointed out that many patients with pseudoxanthoma elasticum are found to have stenosed or obliterated vessels at a comparatively early age and these authors described small oscillographic deflections as a common finding in pseudoxanthoma elasticum. Deformation of finger and toe pulse curves also showed the appearance of altered elasticity of the vessels. Although stenosing arterial processes may show a similar pulse form, in general there is a retarded rise of the initial part of the ascending limb, characterized by a prolonged inclanation time (Bäfverstedt and Lund, 1954). It was further emphasized by these same authors that in early stages of pseudoxanthoma elasticum degenerative changes of the elastic tissue might be localized solely in the vessel wall.

Fischer, Rodman and Lansing (1958) provided evidence that the skin defect of pseudoxanthoma elasticum was located in the elastic fibers and not as had been suggested in the collagen. The authors were able to show in histologic studies that a sufficient number of elastic fibers within the deeper portions of the corium account for the alteration with disruption and fragmentation of these fibers. They further described the appearance of cross bands in some of the distorted fibers in formalin-fixed sections which show a striking similarity to those observed during the process of digestion of normal elastic tissue with elastase.

Electron microscopic studies by Loria, et al., (1958) showed deposits in or on the elastic tissue which simulated or actually represented mineral salts. A high calcium content in areas of elastic tissue degeneration was found also by Finnerud and Nomland (1937) and explained as part of a general pathological process of calcification rather than a causative fundamental process of this specific disease. The actual amount of calcium was studied quantitatively by Lobitz and Osterberg (1950) and was found to be five to seven times as high as in normal elastic fibers of the skin.

The case of Shaffer, et al., (1957) was of

interest in regard to massive calcifications combined with pseudoxanthoma elasticum. Their patient was a 69-year-old white man who suffered from an occlusive vascular disease of the lower extremities with intermittent claudication beginning at the age of 44 years. There were no palpable pulses in either foot and oscillometric readings were almost completely absent in both legs. Extensive skin changes with numerous loose plications were present. The clinical and histopathological diagnosis was pseudoxanthoma elasticum. The soft tissues of both legs appeared hard with multiple plaque-like bony indurations. Auscultation of the heart revealed murmurs similar to those found in cases with calcification of the annulus fibrosis. Laboratory tests for alkaline phosphatase, serum calcium, serum phosphorus and cholesterol were normal. X-ray examination showed extensive calcification of all major blood vessels and of the soft tissues, particularly that of both legs. The ocular fundi in this case showed only slight sclerosis of the retinal vessels and an old choroiditis.

The ocular histologic findings in pseudoxanthoma elasticum have been extensively described by Böck (1938), Hagedoorn (1939) and Verhoeff (1948). The classical clinical findings in angioid streaks are a fine network of brownish-red, grayish or dark brown lines appearing in the posterior part of the eye. These lines often join each other to form a star-shaped figure around the disc. The macular area is often involved with transudates and hemorrhages. The different color of the streaks is thought to be due to the behaviour of the pigment epithelium overlying the ruptures in Bruch's membrane. A generally grayish appearance of the entire fundus has been explained as being due to the abnormal translucency of Bruch's membrane. The pigment epithelium may be found degenerated in areas of larger defects in Bruch's membrane but is generally not involved over the smaller defects or in areas where Bruch's membrane is intact. Except for occasional involvement of the rods and cones, the retina is usually intact.

Osteitis deformans (Paget)

Paget's disease has been described as an entity which may be associated with angioid streaks (Verhoeff, 1928; Rowland, 1933; Terry, 1934) and in a few instances the triad of osteitis deformans, angioid streaks and pseudoxanthoma elasticum has been found (Woodcock, 1952, Shaffer, et al., 1957). In those instances the clinical and pathological findings in regard to the vascular system are comparable to those described under the Groenblad-Strandberg syndrome. A histopathologic description of eyes with angioid streaks in Paget's disease has not been reported as yet.

Atherosclerosis

Atherosclerosis represents another widespread systemic disease which involves simultaneously the vascular system as well as the ocular fundus. The disturbances found in the elastic tissue of the arterial walls differ markedly from those of pseudoxanthoma elasticum. The onset in the latter disease occurs long before the age when atherosclerosis usually begins. The microscopic finding of fat deposition in the intima of the vessels in atherosclerosis is in contrast to the elastic degeneration of pseudoxanthoma elasticum which is located in the media of arteries; and here there is no lipoid deposit at all. The typical feature of atherosclerosis is that of atheromatous plaques situated on the intima of the large arterial blood vessels and loss of elasticity due to a breakdown of elastic elements in the media of arterial walls with calcification.

Lansing (1954) was able to show that the amount of elastica in the vessel media actually does not change with age, but instead there is an alteration in its chemical composition. Such alteration may be related to the amount of available elastase. The in-

ternal elastic membrane seems to play a definite part in regard to the location of vascular lesions in that as long as this membrane remains intact, atherosclerosis is confined to the intima. If this membrane becomes involved (and involvement usually occurs beneath lesions in the intima) the lipid degeneration may destroy the media in the affected areas.

Duff (1954) has repeatedly called attention to the various types of arterial injury which finally result in typical atherosclerotic lesions. In this train of events different histological structures differ in their susceptibility to trauma and elastic tissue appears to be particularly susceptible. Repeated minimal mechanical or chemical trauma, too small to be recognized at the time of their occurrence, appear to be cumulative and finally capable of promoting an atherosclerotic process.

In this respect it is at once apparent that increased vascular pressure is probably of extreme importance in the development of atherosclerotic vascular changes. Variations in degree of acute vascular insults by means of either transitory edema of the vessel wall or severe inflammatory process are probably quantitative in character and depend rather upon duration and intensity of trauma than upon type. Furthermore, systemic factors determine whether a given lesion will occur and local factors in the arterial walls themselves then influence the localization of the lesion. The importance of cholesterol in this respect is well known.

It is not necessary to mention here the classical ocular findings of atherosclerosis, but there are a few reports in the literature which mention the clinical appearance of streaklike formations in the atherosclerotic ocular fundus. The ophthalmologist who is familiar with the clinical picture of angioid streaks will not confuse these "streak-formations" since they differ quite markedly from those of angioid streaks. They are thought to be due to glial proliferation of the retina or perhaps to shadows of vessels produced by obliquely entering light (Fuchs).

Sickle-cell disease

The clinical and general pathologic features of the different types of sickle-cell disease have been extensively reported in the literature. It is a hemolytic disorder, apparently inherited as a Mendelian dominant. Five different groups are recognized and classified according to different electrophoretic patterns or combinations of hemoglobin. Normal, or A hemoglobin associated with hemoglobin S, gives rise to sickle cell trait, which, under normal conditions, is asymptomatic. In sickle cell anemia hemoglobin S-S is present and the full blown picture of the disease usually develops with a shortening of the patient's life span. A combination of S and C hemoglobin may lead to similar manifestations as those observed in hemoglobin S-S disease but usually to a much lesser degree. Hemoglobin C-C is rarely found, shows many target cells in the peripheral blood smear and gives rise to few if any symptoms. In like fashion hemoglobin A-C is clinically asymptomatic.

The full-blown picture of sickle-cell disease is characterized by anemia, joint pain, leg ulcers, abdominal pain and under certain conditions hemolytic crisis. Due to vascular stasis and occlusion the organ involvement is legion. Calcium and hemosiderin are found within the perivascular spaces, particularly in the spleen, causing thickening of the trabeculae and finally extreme atrophy of the organ (autosplenectomy). The bone marrow becomes hyperplastic due to the rapid destruction of erythrocytes and increasing new formation of blood cells; and as a result the medullary space within the bones is usually wide but in more advanced stages may be completely occluded by calcification.

Ingram (1957, 1959) showed that sickling of the erythrocytes is brought about by substitution of one glutamic acid molecule in the acid chain of normal hemoglobin by one

molecule of valine in hemoglobin S, and one molecule of lysin in hemoglobin C. This arrangement causes a difference of electrical charge of the molecule since glutamic acid is negatively charged, valine is electrically neutral and lysin electrically positive.

Ocular manifestations in sickle cell disease have been reported recently in a comprehensive clinical study by Lieb, Geeraets and Guerry. The authors found that there was no significant difference in the ocular pathology, either quantitatively or qualitatively, in sickle-cell anemia (hemoglobin S-S) or hemoglobin S-C disease. In this study the fundus changes were classified according to their severity into four grades.

GRADE I

Increased tortuosity and dilatation of the retinal veins. Mild ischemic areas in the outer periphery of the retina.

GRADE II

Neovascularization and microaneurysms of the venules in the periphery of the retina. Circumscript narrowing of the blood column in peripheral venules.

GRADE III

Retinal hemorrhages and exudates in addition to fundus changes of the preceding grades. Smaller or larger areas of chorioretinal atrophy.

GRADE IV

Retinitis proliferans, vitreous hemorrhage, cholesterol deposits, occasionally papilledema.

An attempt was made to explain the etiology of those ocular lesions by adopting the theory expounded by Wise of neovascularization and its dependence on hypoxia and an unknown tissue factor X.

In regard to the elastic tissue disturbances, findings were first reported by Geeraets and Guerry. Degenerations of Bruch's layer comparable with those described in Groenblad-Strandberg syndrome were demonstrable

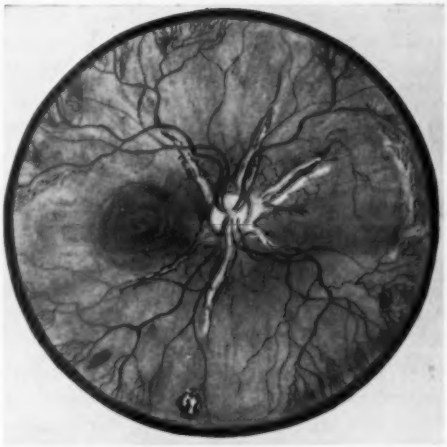

Fig. 1 (Geeraets and Guerry). Fundus of a 26-year-old woman with sickle-cell hemoglobin S-S. There is a Grade IV sickle-cell retinopathy with vasoproliferation and besides this the typical picture of angioid streaks.

clinically as well as in histopathologic studies (fig. 1). In addition, an involvement of the lamina elastica interna in some of the long ciliary arteries was found. It was pointed out that the course of degeneration of elastic fibers in sickle-cell disease was open to speculation but the most likely explanation would be (1) gross involvement of the vascular system by intravascular sickling, low oxygen tension, rapid destruction of erythrocytes, new vessel formation, microaneurysms, hemorrhages, and so forth, or (2) perhaps a familial propensity noted not only in sickle-cell disease but also in the Groenblad-Strandberg syndrome. A third possibility, that of being secondary to a primary existing sickle-cell retinopathy was also mentioned.

The first report on conjunctival capillary pathology in sickle-cell disease was given by the same authors. The in vivo changes mainly consisted of prolonged intravascular stasis and circumscribed dilatations of the capillary wall. Occasionally aneurysmlike excavations remained after normal capillary circulation returned. The site of those changes was most frequently the temporal lower quadrant of

the bulbar conjunctiva and the lower cul-de-sac. The authors stressed the differential diagnostic importance of the clinical picture of sludged blood in comparison with the clinicopathologic findings as observed in patients with sickle-cell disease.

Case report

In the present study histopathologic examinations were carried out on various tissues from 16 autopsy cases of patients who had died from sickle-cell disease. Only such specimens were selected which showed arteries in clean cut cross sections. Those of oblique or parallel sections were discarded from this study. Specimens of 10 autopsy cases of the same age group as in the principle study, but in which the patients had died from accidents, were used as controls. All slides were stained with hematoxylin-eosin, orcein elastic, Verhoeff-van Giesson and alcian-blue stain for mucopolysaccharides.

Previously reported histologic changes of the lamina elastica interna of several long ciliary arteries in eyes of sickle-cell patients were known to consist mainly of doubling and partial absence of elastic fibers. Increase in connective tissue was found in the same areas of the vessel wall where the changes in elastic tissue were present. There was no thickening of the intima.

In two of the examined 16 autopsy cases with sickle-cell disease changes in the lamina elastica interna of medium sized arteries were found. Both cases had died in sickle-cell crisis.

The remaining 14 sickle-cell cases did not show significant changes within the elastic tissue, neither were changes found in the 10 control cases.

Case 1

This 46-year-old Negro had never been seriously ill prior to this hospital admission. He gave a history of being in essentially good health until the past six weeks when he felt slightly weak and noted a mild pain in the right lower chest. On hospital admission pneumonitis of the right lower lobe with pleural reaction was diagnosed. He improved slightly under achromycin therapy.

Physical examination revealed hepatomegaly extending two inches below the right lower costal margin with a surface nodular to palpation. Spleen was not palpable. Auscultation of the heart revealed a Grade II blowing type systolic murmur with punctum maximum at apex and aortic area. There was a moderate scleral icterus. Other findings were of no importance.

Laboratory findings were as follows: Hemoglobin 9.6 mg. percent with 2.9 million RBC, 42,000 WBC and reticulocyte count of 12.2 percent. Positive sickling. Bilirubin direct 10.8 mg. percent and bilirubin total 20.2 mg. percent. Blood urea nitrogen 36 mg. percent, sodium 147 and potassium 4.3. Hemoglobin electrophoresis = hemoglobin S-S.

Several days after admission the patient developed a hemolytic crisis and became semicomatose. In spite of blood transfusions and other extensive therapy the patient's condition deteriorated rapidly death ensuing on the third day after hospital admission.

Gross pathologic examination. Autopsy was performed about two hours after death. External examinations was not remarkable. Gross internal examination showed fibrous stringed adhesions between left anterior upper lobe, posterior lower lobe and the thoracic cage and between right lower lobe and diaphragm.

The spleen was very small and firm. The peritoneum was icteric but smooth.

There was a slight dilatation of the right ventricle of the heart, while the left ventricle was firmly contracted. The endocardium of the right ventricle appeared normal except for a slight gray-white cloudiness at the base of the papillary muscles. The anterior cusp of the tricuspid valve showed a small hemorrhagic area near its lower tip. There were no signs of atherosclerosis of the coronary arteries.

The lungs were congested with adhesions and some mottling. The spleen, weighing only 8.9 gm., was nodular and demonstrated on cut section only two small red foci of splenic tissue, the remainder being yellowish-brown and white in appearance.

The liver showed a nodular surface with a marked increase in consistency throughout. All vessels were dilated and partially packed with blood cells.

The kidneys had a slightly granular appearance. There were submucosal hemorrhages in the lower pole of the right pelvis posteriorly. The vessels were markedly distended. Also the left kidney revealed spotty areas of submucosal hemorrhages as did the bladder mucosa throughout.

The aorta did not show any marked pathologic changes, the intima being smooth and glistening.

A dark red ulcerated area was located in the middle third of the esophagus. Except for several small punctate hemorrhages within the mucosa of the transverse colon there was no other pathology found within the gastrointestinal tract.

The gross pathologic diagnosis was sickle-cell disease, atrophy of spleen (8.5 gm.), liver cirrhosis (2400 gm.) secondary to sickle-cell disease, icterus,

cardiac hypertrophy, mucosal hemorrhages of renal pelvis and bladder.

Microscopic examination showed the architecture of the liver to be distorted by an increase in fibrous tissue. The liver sinusoids were dilated and packed with red sickled cells. Iron stain revealed scattered accumulations of iron pigment granules. A cavernous hemangioma filled with sickled cells was found in several slides.

The spleen was scarred and fibrotic with areas of calcification. A considerable amount of an olive-brown pigment was present which was not doubly refractile and most prominent in the areas of fibrosis. P.T.A. stain showed the sickled cells blue, while the other red cells appeared yellow. In iron stains the olive-brown pigment was found to contain iron.

The kidneys presented local subcapsular accumulations of lymphocytes and plasma cells with fibrosis and thickening of Bowman's capsules. There was scarring which appeared interstitial rather than glomerular. Relatively few glomeruli were completely obliterated. The capillaries were packed with sickled red cells.

Sections of the aorta were without any pathologic alteration.

The mucosa of the gastrointestinal tract showed multiple areas with hemorrhages and acute ulceration with early inflammatory cell infiltration within the mucosa of the esophagus.

Focal hemorrhages were also seen within the cortex of the adrenal gland. Some of the vessels in the capsule showed hyalinization of their walls.

The lungs were congested with slight interstitial thickening, edema and hemorrhages into alveoli. In one pulmonary vessel there was a loosely formed thrombus, probably agonal.

The cerebellum vessels were packed with sickle cells and calcium deposits around the vessels.

Sections of the skin were negative.

The bone marrow presented marked erythroid hyperplasia.

There were no pathologic findings in soft tissue or skeletal X-ray films.

Elastic tissue stains. Sections of all specimens have been stained with elastic tissue stains.

Similar to the findings in sections containing long ciliary arteries and which had been reported previously, the lamina elastica interna of medium-sized arteries, mainly in liver and kidney, showed certain definite abnormalities. The lamina interna was interrupted at numerous sites, but those breaches should not be confused with the normally occurring gaps seen where smaller vascular branches leave the main vessel. At those normal sites of discontinuity, the edges of the lamina elastica interna are usually sharp, there being no destruction, and the direction of the muscle fibers within the vessel wall becomes irregular. In this case, serial sections show areas in which the lamina interna was missing, extending over a much greater distance than that seen in the above mentioned normal instances. The margins of the lamina were irregular with featherlike spreading of thin fibers into the surrounding tissue (fig. 2). Small portions, partly dislocated, were occasionally found in between the two edges of the lamina (fig. 3). The segments close to the zones of discontinuity stained usually more faintly with Verhoeff-van Giesson elastic tissue stain. In many instances the lamina appeared normal in one place, while in another region curled, fragmented and split, resulting in a complete disorganization of the normal structure (fig. 4).

CASE 2

The patient was a 43-year-old Negress with a long standing history of sickle-cell anemia. There had been repeated episodes of severe jaundice since the age of 15 years and known cardiac enlargement for approximately 20 years.

At the time of this last hospital admission she complained of ankle edema and orthopnea of two months' duration. There was jaundice for the same length of time.

On physical examination the eyes were reported as markedly icteric and the retinal vessels as showing increased tortuosity. Other signs of sickle-cell retinopathy were not recorded. The neck veins were greatly distended. A loud systolic murmur was auscultable over all valvular areas with punctum maximum at mitral and tricuspid area. The abdominal

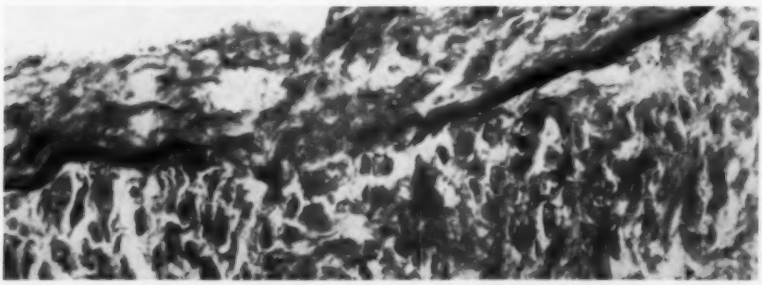

Fig. 2 (Geeraets and Guerry). Discontinuity of the lamina elastica interna of a medium sized artery, the edge of which is split on one side and spread featherlike into the media (Verhoeff-van Giesson, ×400).

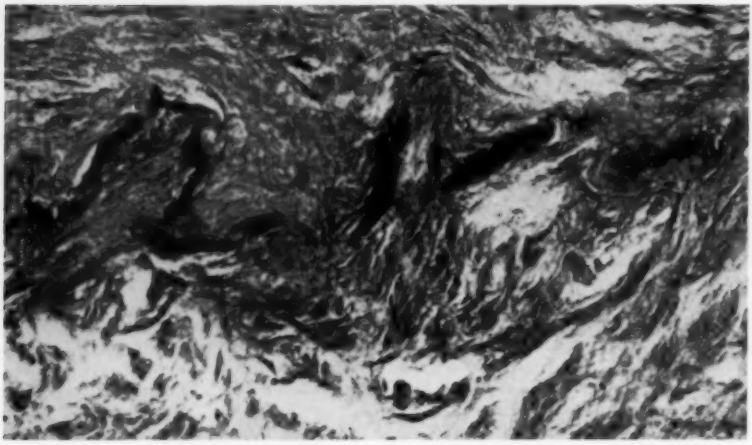

Fig. 3 (Geeraets and Guerry). Interrupted and disarranged parts of the lamina extending over wide areas in several sections (Verhoeff-van Giesson, ×400).

wall was edematous. The liver edge could be palpated down to the iliac crest with signs of ascites. During hospitalization the patient did not react to treatment, her condition worsened and she died in coma.

Laboratory findings. Hemoglobin, 6.0 mg. percent,, RBC 1.6 million, reticulocytes 148 per hundred white blood cells. Sickle-cell prep strongly positive (99.9 percent). Direct bilirubin was 12 and total bilirubin 23.2 mg. percent. Other laboratory findings were not remarkable. Alkaline phosphatase determination was negative.

Gross pathologic and histopathologic examination. Autopsy was performed three hours post mortem. The abdomen showed marked distention

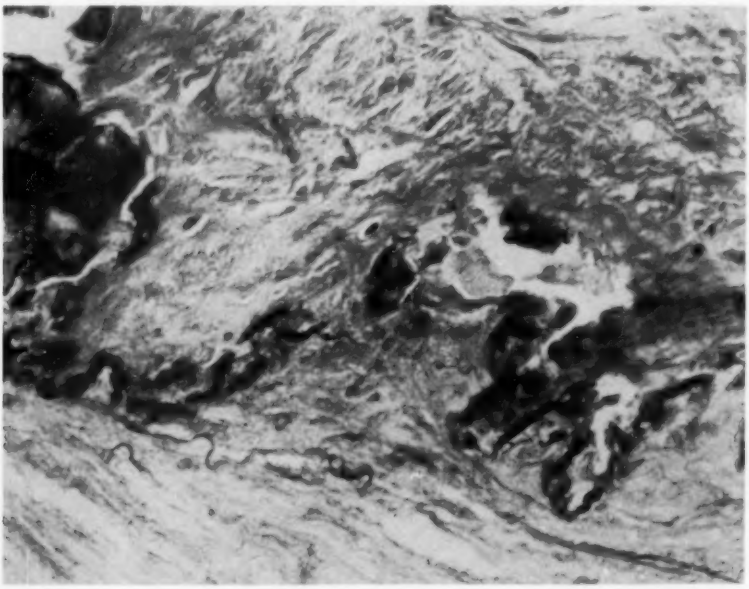

Fig. 4 (Geeraets and Guerry). Plaquelike and curled elastic fibers in areas of destruction of the lamina interna (Verhoeff-van Giesson, ×400).

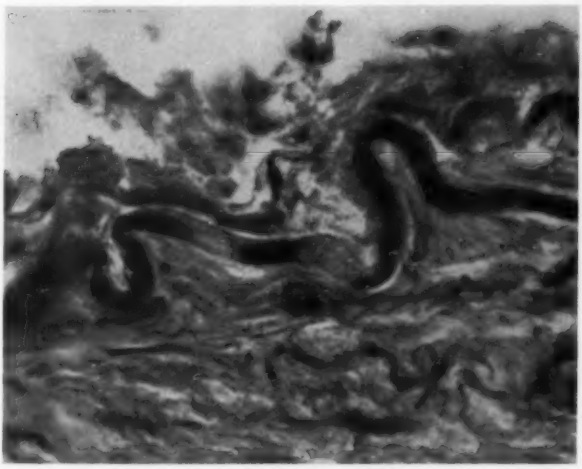

Fig. 5 (Geeraets and Guerry). Circumscribed thickening of the lamina elastica interna with partial loss of staining ability with elastic tissue stains (Verhoeff-van Giesson, ×600).

with an enormously enlarged liver of deep orange color. The lining surface was smooth and tense and of a rather soft consistency with hemosideric changes. Lobules could be seen roughly and these were surrounded by a mild fatty degeneration. Microscopic sections showed severe congestion with packed sickled erythrocytes within the vessels and moderate fatty degeneration.

The spleen weighed 4.3 gm. and measured only 5.2 by 1.4 by 1.1 cm. Its surface was markedly lobulated and contracted with firm consistency. The color was pale grayish. The vessels of this organ were markedly thickened. On histologic sections there was severe fibrosis associated with hemosiderosis and contraction.

The kidneys revealed deep dark pigmentation. The corticomedullary junction was absent. The pyramids were not distinct and stained in a fashion similar to the other portions of the kidney parenchyma. The bladder wall was edematous, trabeculated and contained numerous mucosal hemorrhages. Microscopic sections showed marked hemosiderosis of the kidneys and numerous protein casts.

Except for hemorrhages throughout the pancreas there were no other findings of interest within this organ. The intestinal tract also showed widespread hemorrhages within the mucosa and moderate congestion but no focal lesions.

The lungs showed marked congestion with a few areas of compensatory emphysema. In microscopic sections the alveolar walls were thickened. There were foci of cholesterol deposits. The vessels were distended and packed with sickled red cells.

The heart was moderately enlarged and flabby. Circumscribed pale lesions appeared scattered on its surface. The valves were dilated but the endocardium was smooth.

There were no remarkable findings on sections of the brain and skin sections were negative.

The bone marrow showed hyperplasia of the erythropoetic system.

X-ray examination for soft tissue or skeletal changes was negative.

Elastic tissue stains. Special staining with elastic tissue stains was carried out in order to study the behavior of elastic fibers within the arterial walls. Pathologic features comparable with those described previously in histopathological studies of eyes of sickle-cell patients were found.

As demonstrated in Figures 5 to 8, there were several arteries of medium caliber in pancreas, liver and kidney which showed these pathological changes. The lamina elastica interna in particular was involved. Figure 5 shows the lamina interna stained with Verhoeff-van Giesson elastic tissue stain. There was strongly increased undulation and the elastica showed poor staining properties in circumscribed areas. In several places the lamina interna appeared to be thickened and of a yellowish hue. This thickening was even more pronounced in Figure 6.

Staining with alcian-blue for mucopolysaccharides showed a more intensive staining of the tissue surrounding those areas where swelling and loss of staining ability with elastic tissue stains had been noted. Furthermore, the lamina interna showed doubling in these particular areas (fig. 7). In several areas typical cross-bands were seen (fig. 8) such as those reported by Fischer, Rodman and Lansing as occurring in some elastic fibers in the skin of patients with pseudoxanthoma elasticum. Increase of connective tissue could not be demonstrated in the vessel walls but had been found previously in the walls of long ciliary arteries.

Comment

The following are systemic diseases with ocular fundus pathology and disturbances of the elastica of the vascular system:

1. Groenblad-Strandberg syndrome

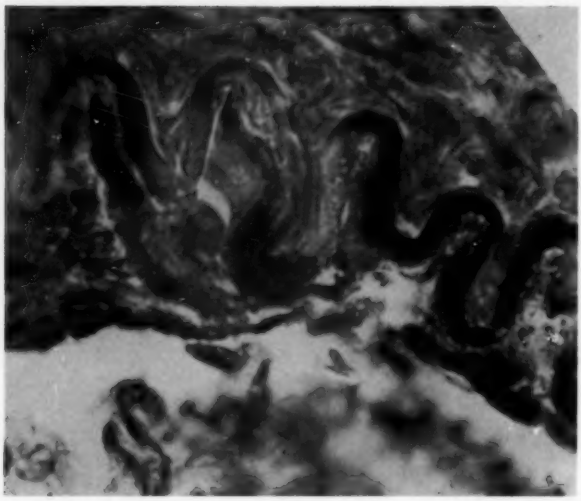

Fig. 6 (Geeraets and Guerry). Marked undulation of the lamina elastica interna with areas of thickening, loss of staining ability and doubling. Those areas staining with Alcian blue showed the presence of higher content of mucopolysaccharide which is not observable in the black and white prints (Verhoeff-van Giesson, × 600).

2. Paget's disease
3. Atherosclerosis
4. Sickle-cell disease

1. *Groenblad-Strandberg syndrome.* The distinct clinical and pathologic features of elastic tissue pathology in Groenblad-Strandberg syndrome are:

Ocular. Angioid streaks due to rupture in Bruch's membrane. Possible calcium deposition within or on the elastic fibers. Irregularity in thickness of Bruch's layer. Possible degeneration of the pigment epithelium in the areas of larger breaks in Bruch's membrane. Vasoproliferation from choroid into subretinal space. Degeneration of the lamina elastica interna of choroidal and long ciliary arteries.

General. Degeneration of the elastic tis-

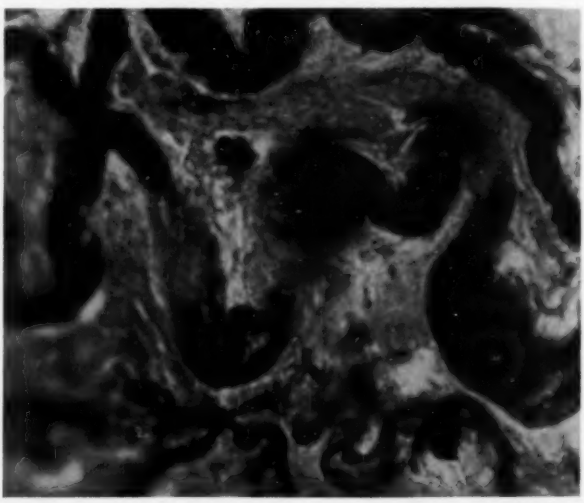

Fig. 7 (Geeraets and Guerry). Doubling and thickening of the lamina elastica interna in higher magnification (Verhoeff-van Giesson, ×900).

Fig. 8 (Geeraets and Guerry). Area with doubling of the lamina elastica interna and typical cross bands within the degenerated fibers (Verhoeff-van Giesson, × 1100).

sue in arterial walls with weak peripheral pulses and calcification which may be demonstrated by x-ray, particularly of the lower extremities. Alteration with disruption and fragmentation of elastic fibres in the deeper portion of the corium.

2. *Paget's disease.* Typical ocular fundus pathology, such as that seen in Goenblad-Strandberg syndrome may be present.

3. *Atherosclerosis.* Elastic tissue disturbances in atherosclerosis are completely different from those seen in Groenblad-Strandberg syndrome.

Ocular. The fundus shows pathology characteristic of arterosclerotic retinopathy. The streaklike lesions which have been confused with true angioid streaks are due to glial proliferation and not to elastic tissue pathology.

General. The site of the vascular lesions is principally confined to the intima. Usually there are fat deposits. The elastic fibers in the media of the arterial wall are involved secondarily and usually only after the tunica elastica interna has been altered.

4. *Sickle-cell disease.* Degeneration of elastic tissue in eyes of patients with sickle-cell disease, recently reported by us, showed striking similarity to the histologic findings in Groenblad-Strandberg syndrome. An incidence of six percent of clinically observable angioid streaks in connection with sickle-cell disease cannot be considered coincidental.

Ocular. Except for the ophthalmoscopically demonstrable fundus lesions of angioid streaks it was shown in histologic studies on three eyes of sickle-cell patients that there were many somewhat similar pathologic features between these eyes and those described in the Groenblad-Strandberg syndrome. It is of interest that the histopathologic studies were carried out on eyes which presented funduscopically sickle-cell retinopathy but no clinically observable angioid streaks.

Microscopically there were defects in Bruch's membrane of different width with sharply cut edges along the margins of the defects. Large areas of Bruch's membrane, particularly in the posterior part of the globe, failed to stain with Verhoeff's elastic tissue stain or orcein. The pigment epithelium was unchanged in the areas of smaller defects in Bruch's membrane but showed complete degeneration in the areas where there were defects of Bruch's layer. The basal layer of the pigmented epithelium and Bruch's layer were separated in several cir-

cumscribed areas by accumulations of colloid material. Proliferative tissue derived from the choroid was found to penetrate through the defects in Bruch's membrane into the subretinal space. Positive iron stain was not demonstrable, which is in contrast to the findings in eyes with angioid streaks as described by Hagedoorn. In addition ruptures, doubling, and featherlike spreading of the lamina elastica interna of choroidal and long ciliary arteries could be demonstrated. All of these findings have been described by Böck and Hagedoorn in their histopathologic studies on eyes from patients with Groenblad-Strandberg syndrome.

GENERAL. The present study would seem to add another facet to the protean complex known as sickle-cell disease, just as the recognition of angioid streaks has done. It is still too early to know, however, the causal mechanism of the defect in the elastic tissue, but it would seem that it must of necessity be related to the extensive pathology resulting from intravascular sickling, stasis and thrombosis which in turn follow in the wake of a consistently low oxygen tension.

On the other hand, if this hypothesis does not prove tenable, it may well be that the relatively high incidence of elastic degeneration in sickle-cell disease is caused by a nutritional-mechanical effect, a disturbance in an enzymatic or otherwise biochemical system, or even to an inherited familial propensity.

There are still many unanswered questions in regard to the biochemical properties of elastic tissue. Perhaps the principal reason for this is the difficulty inherent in obtaining human elastin. Bowes and Kenten (1949) showed that elastin is the only protein in mammalian tissues containing significant quantities of hydroxproline (2.0 percent).

According to Hall, Reed and Turnbridge, polysaccharides and sulfuric acid are intimately associated with protein in elastic tissue. These authors described the stabilizing material, which surrounds the linearly aggregated proelastin, as mixed mucoprotein chains, formed by proelastin units and joined by polysaccharide molecules. It had been assumed that proteolytic enzymes such as trypsin, which has been shown to digest elastic tissue after prolonged treatment, attack the proelastin units themselves. Degeneration of human elastic tissue is brought about by the enzyme elastase. This enzyme was thought to be controlled by an inhibitor present in the sera of normal persons, but absent from those of patients with vascular degeneration. Hall, Reed and Turnbridge stated that elastase could not be obtained from the human pancreas and the authors therefore suggested that in the human probably other organs secrete the enzyme.

Banga and Balo (1953) in their studies on elastin and elastase pointed out that there exist two elastase inhibitors, one in the blood serum and another one in the pancreas. While the latter one dialyses and can be demonstrated in the dialysate, the former one cannot. These authors suggested in earlier experiments that in arteriosclerosis the elastase content of the pancreas would be above normal and therefore attack the elastic fibers in vessel walls.

In later studies Banga and Balo were able to show that there was a significant difference in the content of elastase in the pancreas of young men who died from accidents or various diseases without arteriosclerosis as compared with those who had had arteriosclerosis. In contrast to their original thoughts the former groups contained 208 resp. 155 E.U./gm., while those with arteriosclerosis had only 9± 6.5 E.U./gm. and in 54 percent of the examined cases no elastase could be detected within the pancreas at all. With those findings these authors referred to the fact that the same enzymes which are of decisive significance in decomposing a substance may also catalyze the synthesis of it. Therefore, it was suggested that in arteriosclerosis the disturbance of elastic tissue metabolism might be due to the lack of pancreas elastase and hence prevent regeneration of elastic fibers.

According to Hall, et al., elastin is soluble

in boiling 50-percent urea. The soluble protein is of low molecular weight. During solution polysaccharide and sulfuric acid are released but no free amino acids have been found in the dialysate. These authors stated that the whole question of elastomucin involvement in arteriosclerosis is far more complex than that of a simple enzyme-inhibitor system.

In vitro studies have shown that polysaccharide is liberated following the action of elastase upon elastin. Whether this has anything to do with the increased deposits of mucopolysaccharide in areas of degenerated elastic tissue, as found in vessel walls in sickle-cell disease, remains to be seen. This most likely would point to a situation contrary to the experimental findings of Balo and Banga in arteriosclerosis as mentioned above.

If there is any connection between the two findings of mucopolysaccharides and degenerated elastic tissue, it would either suggest that more elastase is produced, resulting in an elevated action of elastase upon elastin and thus causing elastic fibers to degenerate, leaving behind such deposits of polysaccharide; or elastase inhibitors are decreased, allowing a higher elastase content within the serum and hence increased destruction of elastin. However, this is of course hypothetical and needs further investigation.

While Banga and Balo used different methods to extract human pancreas in order to study elastase action, Robert and Samuel (1957) reported on a spectrophotometric method for measuring the rate of solution of elastin by determination of liberated dye appearing in the supernate after a certain measured time of hydrolysis. The authors prepared azoelastin in a similar way to that described by Oakley, et al., for preparation of azocollagen. The rate of solution of azoelastin by elastase was defined as an azoelastic unit (E.U.), that is, the quantity of enzyme dissolving 1 mgm of azoelastin under the given conditions (30 min, at 35°C. with a pH of 9.6). To demonstrate the inhibitory action of a certain substance within the serum, 0.25 ml. serum was added to the azoelastin before the enzyme was added. Among the serum proteins neither albumin, gamma globulin nor seromucoid showed any inhibitory action. While beta-lipoprotein did not act as an inhibitor, alpha-lipoprotein and the heavy residue which is free of lipoprotein inhibited elastolysis strongly.

Since these authors found that the degree of inhibition of elastolysis and proteolysis was the same, they concluded that the mechanism of inhibition is independent of the nature of the substrate and explained therefore the action of enzyme and inhibitor as a direct interaction. They also found that there exists a relationship between the inhibition of the proteolytic activity of elastase and that of trypsin, although to a lesser extent than that between the inhibition of proteolytic activity and elastolytic activity of elastase. Therefore, it might be possible that one of the inhibitors of elastase is identical with the inhibitor of trypsin. A more detailed description of the method can be found under the original article of the authors.

This relatively uncomplicated method appears to be worthwhile for further investigations on the above mentioned conditions, particularly Groenblad-Strandberg syndrome and sickle-cell disease.

In comparing the findings in the lamina elastica interna of several arteries of the two cases reported here, the question arises as to which extent the two pictures might be caused by the same pathologic condition. While the destruction of the elastic fibers in Case 2 seems to be in an active stage, the histopathologic features in Case 1 appear more or less to be in a resting or dormant stage. An answer to the problem as to how far the pathology of sickle-cell disease may be involved with elastic tissue pathology cannot be given here. Some of the features described here suggest an involvement of enzymatic action, since similar changes in the structure of elastic fibers have been observed in vitro when elastase acts upon elastin. It cannot be decided, however, at this time

whether intraocular as well as general elastic tissue degeneration in sickle-cell disease is coincidental or whether there is a true causative relationship.

Further biochemical studies in regard to the above-mentioned questions are in progress and will be reported elsewhere.

Summary

A comparison of systemic diseases with involvement of elastic elements of the vascular system and angioid streak formation in the ocular fundus is given.

Previously reported findings of angioid streaks in sickle-cell disease and their histopathologic characteristics have been described.

The pathology in two cases with degeneration of elastic fibers in arterial walls in sickle-cell patients is reported. Theories of elastic tissue degeneration in regard to biochemical properties and disturbances are discussed along with their possible adaptation to the changes noted in sickle-cell disease.

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References

Bäfverstedt, B., and Lund, F.: Pseudoxanthoma elasticum and vascular disturbances with special reference to a case in a nine-year-old child. Acta derm. vener., Stockh., **35**:438, 1955.

Balo, J., and Banga, I.: The elastolytic activity of pancreatic extracts. Biochem. J., **46**:484, 1950.

———: Changes in the elastase content of the human pancreas in relation to arteriosclerosis. Acta Physiol. Acad. Sc. Hung., **4**:187, 1953.

———: Elastase and elastase inhibitor. Nature, **164**:491, 1949.

Blazer, F.: Récherches sur les charactères anatomiques du xanthelosma. Arch. de physiol., **4**:65, 1864.

Benedict, W. L.: The pathology of angioid streaks in the fundus oculi. J.A.M.A., **109**:473, 1937.

Böck, J.: Zur Klinik und Anatomie der gefässähnlichen Streifen im Augenhintergrund. Ztschr. f. Augenh., **95**:1, 1938.

Carlborg, U.: Studies of circulatory disturbances, pulse wave velocity and pressure pulses in larger arteries in cases of pseudoxanthoma elasticum and angioid streaks. Acta Med. Scand., Supp. 151, 1944.

Duke-Elder, W. S.: Textbook of Ophthalmology. St. Louis, Mosby, 1941, v. 3, p. 2602.

Finnerud, C. W., and Nomland, R.: Pseudoxanthoma elasticum (proof of calcification of elastic tissue; occurrence with and without angioid streaks of the retina). Arch. Dermat. and Syph., **35**:653, 1937.

Fisher, E. R., Rodman, G. P., and Lansing, A. I.: Identification of the anatomic defect in pseudoxanthoma elasticum. Am. J. Path., **5**:977, 1958.

Geeraets, W. J., and Guerry, D.: Angioid streaks and sickle-cell disease. Am. J. Ophth., **49**:450 (Mar.) 1960.

———: Clinical observations on conjunctival capillaries with special reference to sickle-cell disease. Southern M. J., in press.

Goodman, G., von Sallmann, L., and Holland, M. G.: Ocular manifestations of sickle-cell disease. A.M.A. Arch. Ophth., **58**:655, 1957.

Groenblad, E.: Angioid streaks: Pseudoxanthoma elasticum. Acta Ophth., **7**:329, 1929.

———: Angioid streaks: Pseudoxanthoma elasticum. Der Zusammenhang zwischen diesen gleichzeitig auftretenden Augen und Hautveränderungen. Acta Ophth., **10**: Suppl. 1, 1932.

Hagedoorn, A.: Angioid streaks. Arch. Ophth., **21**:746; 935, 1939.

Hale, C. W.: Histochemical demonstration of acid polysaccharides in animal tissue. Nature, **157**:802, 1946.

Hall, D. A., Reed, R., and Tunbridge, R. E.: Structure of elastic tissue. Nature, London, **170**:264, 1952.

Harden, A. S., Jr.: Sickle-cell anemia: Changes in the vessels and in the bones. Am. J. Dis. Child., **54**:1045, 1937.

Having, E., and Itano, H.: Electrophoretic studies of globin prepared from normal adult and S-C hemoglobin. Proc. Nat. Acad. Sc., **39**:65, 1953.

Hoffmann, D.: Kardiovasculäre Erkrankungen beim Strandberg-Groenblad Syndrom. Zschr. menschl. Vererb., **33**:389, 1956.

Holloway, T. B.: Angioid streaks. Tr. Am. Ophth. Soc., **25**:173, 1927.

Ingram, V. M.: Gene mutations in human hemoglobin. Nature, London, **180**:326, 1957. Scientific American, Jan., 1959.

Itano, H. A.: Interpretation of electrophoretic, solubility and denaturation data in the study of hemoglobin differences. Fed. Proc., Balt., **16**:748, 1957.

Kaplan, L., and Hartman, S. W.: Elastica disease: Case of Groenblad-Strandberg syndrome with gastrointestinal hemorrhage. A.M.A. Arch. Int. Med., **94**:489, 1954.

Kat, W., and Prick, T. T. G.: A case of pseudoxanthoma elasticum with anatomicopathologic irregularities of the thyroid arteries. Psychiat. en neurol. bl., **44**:417, 1940.

Kimmelstiel, P.: Vascular occlusions and ischemic infarction in sickle-cell disease. Am. J. M. Sc., **216**: 11 (July) 1948.

Knapp, H.: On the formation of dark angioid streaks as an unusual metamorphosis of retinal hemorrhage. Arch. Ophth., **21**:289, 1892.

Lambert, R. K.: Paget's disease with angioid streaks of the retina: Report of two cases. Arch. Ophth., **22**:106, 1939.

Lieb, W. A., Geeraets, W. J., and Guerry, D.: Sickle-cell retinopathy. Acta Ophth., Suppl. 58, Dec. 1959.

Lobitz, W. C., Jr., and Osterberg, A. W.: Pseudoxanthoma elasticum: Microincineration. J. Invest. Dermat., **15**:297, 1950.

Loria, P. R., Kennedy, C. B., Freeman, J. A., and Henington, V. M.: Pseudoxanthoma elasticum (Groenblad-Strandberg syndrome): A clinical, light-, and electron microscopic study. A.M.A. Arch. Derm., **76**:609, 1957.

McKusick, V. A.: Heritable disorders of connective tissue: VI. Pseudoxanthoma elasticum. J. Chronic Dis., **3**:263, 1956.

Mostofi, F. K., Vorder Bruegge, C. F., and Diggs, L. W.: Lesions in kidneys removed for unilateral hematuria in sickle-cell disease. A.M.A. Arch. Path., **63**:336, 1957.

Neel, J. V.: The clinical detection of the genetic carriers of inherited disease. Medicine, **26**:127, 1947.

Pauling, L., Itano, A. H., Singer, S. J., and Wells, I. C.: Sickle-cell anemia: A molecular disease. Science, **110**:543, 1949.

Plange, O.: Pigmentstriae with secondary changes in the retina after hemorrhage. Arch. Ophth., **21**: 282, 1892.

Prick, T. T. G.: Doctoral treatise Maastricht, 1938.

Rinehart, J. F., and Abul-Haj, S. K.: An improved method for histologic demonstration of acid mucopolysaccharides in tissues. Arch. Path., **52**:189, 1951.

Robert, L., and Samuel, P.: Méthode spéctophotométrique pour le dosage de l'inhibiteur sérique de l' élastase. Ann. biol. clin., **15**:453, 1957.

Rowland, W. D.: Angioid streaks. Am. J. Ophth., **16**:61, 1933.

Scheie, H. G., and Freeman, N. E.: Vascular disease associated with angioid streaks of the retina and pseudoxanthoma elasticum. Arch. Ophth., **35**:241, 1946.

Scheie, H. G., and Hogan, T. F.: Angioid streaks and generalized arterial disease. A.M.A. Arch. Ophth., **57**:855, 1957.

Shaffer, B., Copelan, H. W., and Beerman, H.: Pseudoxanthoma elasticum; A cutaneous manifestation of a systemic disease (Paget's disease and arteriosclerosis). A.M.A. Arch. Derm., **76**:622, 1957.

Siegrist, A.: Beitrag zur Kenntnis der Arteriosklerose der Augengefaesse. Internat. Ophth. Kong. Utrecht, 1899, p. 131.

Terry, T. L.: Angioid streaks and osteitis deformans. Tr. Am. Ophth. Soc., **32**:555, 1934.

Turner, R. H., and Bowers, C. Y.: The minute blood vessels in disease. Am. J. Med., **18**:169, 1955.

Urbach, E., and Wolfram, S.: Ueber Veränderungen des elastischen Gewebes bei einem autoptisch untersuchten Falle von Groenblad-Strandbergschern Syndrom. Arch. Derm. & Syph., **176**:167, 1938.

Verhoeff, F. H., and Sisson, R. J.: Basophilic staining of Bruch's membrane. Arch. f. Ophth., **55**:125, 1926.

Verhoeff, F. H.: Histologic findings in a case of angioid streaks. Brit. J. Ophth., **32**:531, 1948.

Wagner, B. M., and Shapiro, S. H.: Application of alcian-blue as a histochemical method. Lab. Invest., **6**:472, 1957.

Wise, G. N.: The mechanism of retinal neovascularization. Am. Acad. Ophth., 1958.

Woodcock, C. W.: Pseudoxanthoma elasticum, angioid streaks of retina and osteitis deformans. A.M.A. Arch. Dermat. & Syph., **65**:623, 1952.

Zimmerman, L. E.: Application of histochemical methods for the demonstration of acid mucopolysaccharides to ophthalmic pathology. Tr. Am. Acad. Ophth., **62**:697, 1958.

———: Further histochemical studies of acid mucopolysaccharides in the intraocular tissues. Am. J. Ophth., **45**:299, 1958.

FURTHER STUDIES ON VITREOUS RESIDUAL PROTEIN*

I. Composition and solubility studies

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Residual protein of the vitreous body has been classified as a collagen since 1894[1,2] when it was found that solutions prepared by boiling the residual protein in water gelled when cooled. Pirie, Schmidt and Waters[3] recovered a gel from a solution of ox residual protein in hot dilute hydrochloric acid and offered considerable physical and chemical evidence that it was a collagen. Matolsty[4] suspended fragmented ox residual protein in a salt solution and recovered "vitrosin" after acidification of the solution. While such heat and acid treatments yield chemically "purified" products, there are modifications of physical structure and changes in pattern of response to specific proteolytic enzymes.

The composition of vitreous residual protein differs from that of the more typical collagens by a higher sugar content and lower amounts of nitrogen and hydroxyproline even when allowance is made for the sugar. According to a recent survey[5] no mammalian collagen contains more than one percent of sugar. As Table 1 shows, sugars have been found in residual protein in the concentration range of three to eight percent. Dische and Zelmanes[6] found glucose and galactose present in equal amounts.

Various sorts of fibrils have been reported to be present in residual protein.† Bembridge, Crawford and Pirie[10] differentiated vitreous fibrils into two groups on the basis of response to proteolytic enzymes and noted the respective location in the vitreous body of each type. They also noted that the protein was more concentrated in the peripheral than in central vitreous, a fact also reported by Balazs.[11] We[8] found that trypsin dissolved part of our residual protein preparation readily and only slightly attacked the remaining portion. Pirie and Van Heyningen[12] suggest that residual protein may be a mixture of collagen and another protein rich in carbohydrate.

Analytical studies of the collagens are hampered by the insolubility of such proteins although certain of them have limited solubilities in neutral salt solutions and acidic or basic buffers.[13-19] The insolubility of residual protein precludes the use of the classical purification sequence of solution, clarification and precipitation.

In this paper we describe a "standard" preparation of bovine residual protein and its concentration in the vitreous body. Analyses for characteristic components are reported. Several solvents were used in attempts to dissolve part of residual protein to see if any fractionation occurred or if sugars could be extracted.

Methods and Materials

Residual protein. Steer eyes were obtained within four hours after slaughter of the animals and the secondary vitreous was obtained as follows. An equatorial cut was made through the coats of the eye and the entire anterior portion of the eye, with the vitreous attached, was lifted away from the posterior portion. The sclera was folded back over the cornea leaving the vitreous hanging free. The vitreous was cut away along a line two to three mm. below the ora serrata to obtain only secondary vitreous. The isolated vitreous preparations were rinsed free of adherent bits of tissue

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† Reviewed in following paper. See pages 232-236.

TABLE 1

ANALYSIS OF RESIDUAL PROTEIN

Material Analysed	% Nitrogen	% HO-Proline	% Sugar	Reference
Vitrosin*	15	11.7	8	4
Homogenized residues	11.1–13.7	9.1–10.0	—	7
Residual protein†	12	—	3–7	3
Residual protein purified	14.8	—	6	3
Residual protein	—	—	4.4	6
Residual protein	11.5	11.3	Present	8
Residual protein after trypsin	14.7	12.5	Present	8
Typical Collagen Kangaroo Tail	17.8	13.0		9
		13.9	0.5	‡

* Material resuspended from acid.
† Recovered from HCl solution pH 1.8 at 100° C.
‡ Our work, unpublished.

by swirling in water. Any particles visible against both dark and light backgrounds were picked away. The residues were then collected by high speed centrifugation (60,000-100,000 × G) for 90 minutes. The pellets so obtained were soaked in a large volume of water for 24 to 48 hours and unless otherwise noted were treated with hyaluronidase to remove traces of hyaluronic acid. In a few specific cases the cleaned vitreous bodies were ground in an electrically driven homogenizer prior to centrifugation.

Weights. All weights are reported on a dry weight basis. The residues for analysis were brought to constant weight by drying in a 90°C. oven and cooling over an efficient desiccant. Since the material is extremely hygroscopic[6] weighings were made within 15 seconds after removal of the samples from the desiccator.

Elementary analyses. Carbon, hydrogen, oxygen, sulfur, phosphorus and ash analyses were made by an outside laboratory.*

Hydrolysis procedures. Samples to be analyzed for nitrogen and hydroxyproline were heated with 6 N HCl (about 10 mg. residue per ml. acid) in a sealed tube at 95°C. for 16 hours and sugar analyses were made upon samples hydrolyzed in 0.5 N H_2SO_4 under similar conditions. Hexosamine was determined upon similarly handled residues heated with 2 N HCl. No prior hydrolysis was done when testing for hexuronic acids.

Nitrogen determinations were made using the micro-Kjeldahl digestion procedure and reagents of Grunbaum, Shaffer and Kirk[20] while the diffusion and titration were done in a micro-Conway apparatus.

Hydroxyproline was determined by the method of Martin of Axelrod[21] with slight modifications.

Hexosamines were measured by the method of Boas,[22] omitting the resin absorption pretreatment.

Hexuronic acid determinations were made by the carbazol method of Dische.[23] The samples of either enzyme supernatant solution or residual protein, one mg. per analysis, were hydrolyzed directly in the test.

Sugars were determined by the indol or α-naphthol methods as described by Dische.[23] The indol reaction measures uronic acids in addition to hexoses while the α-naphthol reaction measures only hexoses. Results are reported as glucose.

Lipids. Eighteen mg. of residual protein were extracted with 25 ml. of 1:1 alcohol-ether solution for several hours in a Soxhlet apparatus.

Gelatinization. Residual protein at a concentration of about 0.5 percent was twice extracted with water by heating in an autoclave at 15 pounds pressure for 45 to 60 minutes.

* Microchemistry laboratory, University of California, Berkeley.

Hot acid treatment. One percent by weight of residual protein was twice extracted in 0.01 N acetic acid in sealed tubes at 90°C.

Solubility in cold solvents. The residual protein preparations were extracted with large volumes of 0.02 M citrate buffer pH 3.8, 0.01 M acetic acid pH 3.9, 0.2 M borate buffer pH 7.8, 0.9 percent and 5.0 percent sodium chloride. Also, whole vitreous bodies were extensively washed in 2.0 percent sodium chloride before the residues were collected. Residues were soaked in 2 M calcium chloride and 6 M urea for periods of 48 hours.

Results and Discussion

I. Analysis of bovine residual protein

Amount of residual protein. Many determinations were made on individual samples, pooled specimens, those washed in water over long periods, those treated with hyaluronidase and specimens collected after thorough homogenization in water. The great majority yielded values of 10.0 to 10.5 mg. percent of whole fresh vitreous weight with the range being 8 to 11 mg. percent.

Elementary analysis gave the following average composition of typical pooled specimens: carbon 49 percent, hydrogen 7.0 percent, oxygen 29 percent, nitrogen 14.6 percent, sulfur less than 2.0 percent, phosphorus less than 0.1 percent, ash less than 1.0 percent.

Component analysis showed 12.5 percent hydroxyproline, 4.0 to 7.0 percent sugars (glucose and galactose in about equal quantities by chromatography) fats (alcohol-ether extract) less than 1 percent, hexosamine 0.4 to 0.6 percent and hexuronic acid about 0.2 percent.

II. Solubility studies

Gelatinization. Two parallel experiments were made. In each, the pooled aqueous extracts of autoclaved residual protein contained 90 percent of the original material; the insoluble remaining material was dark colored. One of the solutions was concentrated to contain about 2.0 percent protein, at which point it gelled.

Each of the solutions was analyzed both directly and again after dialysis against water. For sample G, 89 percent of the solubilized protein remained after dialysis. Table 2 shows the results of this work.

Although this treatment split some bonds of the protein molecule as evidenced by the loss of weight during dialysis, the relative amounts of nitrogen, hydroxyproline and sugars were not appreciably changed.

Hot acid treatment left 9.0 percent of dark material undissolved. Two thirds of the solubilized material was lost during dialysis of the solution. Table 3 shows a comparison of the compositions of the original insoluble residual protein and the nondialyzable solubilized protein.

Pirie, Schmidt and Waters used HCl at at pH 2.0 at 100°C. to dissolve their residual protein in a similar experiment. While substantial amounts of material were lost by di-

TABLE 2

Gelatinization of residual protein

	Sample D		Sample G	
	Solution before Dialysis	Solution after Dialysis	Solution before Dialysis	Solution after Dialysis
% of starting material	86	89×86=77	91	89*×91=81
% Nitrogen	14.8	10.4	14.2	11.3
% Hydroxyproline	12.0	7.2	11.1	8.6
% Sugars	5.6	4.5	4.9	4.2
HO-Pro/N	0.81	0.71	0.78	0.76
Sugar/N	0.38	0.43	0.34	0.37

* Assumed to be the same as Sample D.

TABLE 3

HOT ACID TREATMENT OF RESIDUAL PROTEIN

	Original Residual Protein	Acid Soluble Protein Solution Remaining after Dialysis	Dialyzed/ Original
Weight	100%	31%	
% hyaluronic acid	0		
% nitrogen	13.2	11.5	87
% hydroxyproline	10.8	10.1	93
% sugars	5.4	3.9	72
OH-Prol/N	0.82	0.88	
Sugar/N	0.41	0.34	

alysis, here again no fractionation occurred.

Extraction with cold solvents. Unlike skin or tissue collagens, vitreous residual protein does not contain fractions, detectable by weight loss, which are soluble in citrate, acetate or borate buffers or in 0.8 to 5.0 percent sodium chloride. Treatment with calcium chloride and urea solutions caused some weight loss but the composition of the remaining protein was unchanged. These two reagents have been used to extract sugars from proteins[24] and urea has been claimed to dissolve proteins[25,26] but no such effect was found on residual protein.

SUMMARY

A standard procedure for preparing the insoluble proteins of bovine vitreous body is described. A yield of about 10 mg. percent of whole vitreous is obtained. Analysis shows nitrogen 14.5 percent, hydroxyproline 12.5 percent and sugars 4.0 to 7.0 percent as typical composition.

Bovine residual protein is confirmed as being a unique collagen in having a high content of sugars. None of the methods tested for extracting sugars or fractionating the compound diminished the relative amount of sugars, or significantly changed the ratio of sugar to nitrogen and hydroxyproline. Hence the sugar appears to be an intimate part of the collagen.

Residual protein is not soluble in the salts and buffers tested although it can be dissolved in hot dilute acid or by autoclaving with water.

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REFERENCES

1. Mörner, C. T.: Ztschr. f. Physiol. Chem., **18**:233, 1894.
2. Young, R. A.: J. Physiol., **16**:325, 1894.
3. Pirie, A., Schmidt, G., and Waters, J. W.: Brit. J. Ophth., **32**:321, 1948.
4. Matolsty, A. G.: J. Gen. Physiol., **36**:29, 1952.
5. Gross, J., Dumsha, B., and Glazer, N.: Biochim. & Biophys. Acta, **30**:293, 1958.
6. Dische, Z., and Zelmanes, G.: Arch. Ophth., **54**:528, 1955.
7. Woodin, A. M., and Boruchoff, S. A.: J. Biophys. & Biochem. Cytol., **1**:489, 1955.
8. Suran, A. A., and McEwen, W. K.: Am. J. Ophth., **42**:338 (Oct. Pt. II) 1956.
9. Neuman, R. E.: Arch. Biochem., **24**:289, 1949.
10. Bembridge, B. A., Crawford, G. N. C., and Pirie, A.: Brit. J. Ophth., **36**:131, 1952.
11. Balazs, E. A.: XVII Conc. Ophth., 1954, 1019, 1955.
12. Pirie, A., and Van Heyningen, R.: The Biochemistry of the Eye. Springfield, Ill., Thomas, 1956, p. 247.
13. Cooper, D. R., and Johnson, P.: Biochim. & Biophys. Acta, **26**:317, 1957.
14. Gross, J., Highberger, J. H., and Schmitt, F. O.: Proc. Nat. Acad. Sc. U.S., **41**:1, 1955.
15. Jackson, D. S., and Fessler, J. H.: Nature, **176**:69, 1955.
16. Nageotte, J.: Compt. Rend. Acad. Sc. Paris, **184**:115, 1927.
17. Burton, D., et al.: Nature, **176**:966, 1956.
18. Bowes, J. H., Elliot, R. G., and Moss, J. A.: Biochem. J., **61**:143, 1955.
19. Orekhovich, V. N., and Shpikiter V. O.: Science, **127**:1371, 1958.
20. Grunbaum, B., Shaffer, F. L., and Kirk, P. L.: Anal. Chem., **24**:1487, 1952.
21. Martin, C. J. and Axelrod, A. E.: Proc. Soc. Exper. Biol. & Med., **83**:461, 1953.
22. Boas, N. F.: J. Biol. Chem., **204**:553, 1953.
23. Dische, Z.: Methods in Biochemistry. New York, Interscience, 1955, v. 2, p. 313.
24. Wood, G. C.: Biochem. J., **55**:XXIV, 1953.
25. Bowen, T. J.: Biochem. J., **55**:766, 1953.
26. Bairati, A., and Paterno, M.: Cited in Chem. Abstracts, **49**:12584, 1955.

FURTHER STUDIES ON VITREOUS RESIDUAL PROTEIN*

II. Enzymatic fractionation

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The relationship between structure and the chemical nature of the vitreous is still not clear. At the microscopic level of investigation workers using phase contrast microscopy[1-4] and electron microscopy[5-8] have described systems containing more than one type of fibril in their various residual protein preparations. Using the phase contrast microscope on portions of fresh vitreous body, Bembridge, Crawford and Pirie[1] observed a unique attack by each of the two enzymes, collagenase and trypsin, upon two distinct types of fibrils. However, Sugiura[6] detected no change in the appearance of residual protein under the electron microscope following treatment with trypsin. We[9] have reported that, on the basis of weight loss, trypsin differentiated residual protein into at least two fractions; one 30 to 40 percent by weight being removed by an initial trypsin treatment, the remaining portion being only slowly diminished in weight by continued applications of trypsin.

While vitreous residual protein is considered to be a collagen it differs from other collagens in two important respects, its unusually high sugar content (glucose and galactose[10]) and its susceptibility to attack by enzymes other than specific collagenases. Native collagen from other sources, such as tendon, is only slightly broken down by trypsin,[11] while residual protein loses weight upon treatment with trypsin and, as will be seen here, with other enzymes.

For this paper we have studied the effects of various enzymes upon our "standard" preparations of bovine residual protein.* It is not clear at this time how the two (or more) fiber types observed may differ in chemical nature or specificity with regard to enzymes. Pirie and Van Heyningen[12] speculate that the sugar may be part of another protein associated with collagen in residual protein. We have wondered if residual protein were a compound fiber with a collagen core and mucoprotein shell or if the polysaccharide might be an interfibrillar cement. For the purpose of differentiating such protein types or of removing polysaccharide from collagenlike protein we have employed several proteolytic enzymes and one glucosidic enzyme mixture.

Trypsin and collagenase were used in continuation of our previous work.[9] Emulsin, which is a mixture of sugar splitting enzymes, was employed with the objective of removing the sugars. Konno and Altman[13] have reported that carboxypeptidase splits an intact polysaccharide-amino acid complex from muscle collagen, so this enzyme was used as a potential means of fractionating residual protein. We used chymotrypsin to compare its effects with trypsin and because it has recently been reported to have "zonulytic" action. Elastase was used to see if any of our insoluble fibrous protein might be susceptible to it.

Methods and Materials

Bovine vitreous residual protein was collected as previously described.* Analyses were also done in the same manner. Samples were brought to constant weight in a vacuum desiccator at room temperature.

Enzymes. All enzymatic hydrolyses were carried out for 16 hours at 37°C. in covered

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* See preceding paper, pages 228-231.

tubes containing a drop of toluene to control bacterial contamination.

*Hyaluronidase.** One hundred TRU/ml of 0.1 M acetate buffer pH 5.4 was used for each mg. residual protein treated.

Trypsin. One mg. of Tryptar® (Armour) per ml. of 0.2 M borate buffer pH 7.8 was used for 1.0 to 2.0 mg. residual protein.

Chymotrypsin. Chymotrypsin (Worthington) was used under similar conditions.

Carboxypeptidase. One-tenth ml. of a commercial suspension (Nutritional Biochemicals Corp.) was mixed in 1.0 ml. 0.06 M phosphate buffer pH 7.4 containing 1.2 M lithium chloride[14] and was used to treat 18 mg. of residual protein.

Collagenase. One mg. of Cl. perfringens (Welchii) collagenase† per ml. of 0.2 M borate buffer pH 7.8 was used to treat each mg. of residual protein and 1.0 mg. Cl. histolyticum collagenase‡ was used under similar conditions for 3.0 mg. residual protein.

Emulsin. Five mg. of emulsin, a mixture of glucosidic enzymes (Nutritional Biochemicals Corp.), in 5.0 ml. of 0.1 M acetate buffer pH 5.2 was used to hydrolyse 18 mg. residual protein.

Elastase. Approximately 50 mg. of elastase in 0.5 ml. of a commercial suspension (Worthington elastase 2 X crystallized) was diluted to 5.0 ml. with 0.2 borate buffer pH 7.8 and 1.0 ml. of this was used with 17 mg. residual protein.

Chromatography was done as described previously.[9]

Results

Regarding each enzyme, special remarks will be made in the text, otherwise analytical values are summarized in Table 4 at the end of this section.

Trypsin. The residues were treated prior to trypsin, with hyaluronidase until analysis showed less than 0.5-percent hexosamine present. In four separate series of experiments we confirmed our previous finding[9] that treatment of residual protein with trypsin effects an initial loss in weight, here 15 to 24 percent, and that smaller losses continued with repeated trypsin applications. The samples which were dehydrated at successive steps lost somewhat more weight than those which were kept wet throughout the procedures. Table 1 shows the composition of these samples before and after treatment with trypsin. The material dissolved by trypsin was found to have lower percentages of hydroxyproline and sugars than either our initial residual protein or the insoluble remaining protein as shown in Table 2. These data show that more sugar than hydroxyproline remains with the insoluble protein after repeated trypsin treatments.

It was found, by chromatography and analysis for hydroxyproline, that only about 10 percent of the hydroxyproline in the supernatant solution was dialyzable or detectable before acid hydrolysis. Proline could not be detected on chromatograms before acid hydrolysis while 10 other amino acids or small peptides were visualized.

Emulsin dissolved part of the residual protein containing 4.4 percent sugars.

Collagenase, Cl. perfringens. For each treatment of residual protein with this enzyme, a stepwise weight loss of about 60 percent was noted. Analysis of the residues following one, two and three enzymic hydrolyses yielded values for nitrogen and hydroxyproline in the amount of 2.0 to 4.0 percent, while the supernatant solution of hydroxyproline was about 10 percent. In this instance, we were progressively separating collagen from noncollagenous material as well as accumulating the inevitable impurities attendant upon working with insoluble materials. Cl. histolyticum collagenase dissolved 93 percent of the residual protein. The supernatant solution had only a slight amount of free hydroxyproline, 0.4 percent, while after acid hydrolysis 12.6 percent was measured. No proline or hydroxyproline

* Couresy Wyeth, Inc.
† Courtesy Wellcome Research Laboratories, Kent, England.
‡ Courtesy Lederle Laboratories.

TABLE 1

EFFECT OF TRYPSIN ON RESIDUAL PROTEIN

Sample	No. Trypsin Treatments	Cumulative % Weight Remaining	Nitrogen	Hydroxy-Proline	Hydroxy-Proline/N	Sugar	Sugar/N	Comment
F (wet)	0	100	11.5*	10.9*	0.95	—	—	*Assume same at start as Sample G
wet	2	76†	14.3	12.7	0.89	Present	—	
dried	3	56	14.6	12.4	0.85	Present	—	†Assume same % as G
G (dried)	0	100	11.5	10.9	0.95	Present	—	
dried	2	76	14.7	12.5	0.85	Present	—	
dried	3	52	14.6	12.3	0.84	Present	—	
3 (wet)	0	100	14.1	10.9	0.78	5.5	0.39	‡Assume same at start as Sample 4
wet	1	85‡	14.7	12.0	0.82	5.0	0.34	
wet	2		16.1	13.1	0.81	6.3	0.39	
wet	3		12.7	9.3	0.73	6.0	0.47	
dried	4	73	12.1	11.7	0.89	6.6	0.55	
4 (dried)	0	100	14.0	10.4	0.74	5.8	0.41	
dried	1	85	14.1	13.3	0.95	7.0	0.50	
dried	2	75	14.3	12.2	0.85	5.7	0.40	
dried	3	57	15.8	15.4	0.97	6.6	0.42	
dried	4		12.2	10.8	0.56	7.8	0.64	

could be seen on chromatograms prior to acid hydrolysis.

Elastase removed a large amount of residual protein leaving behind a greyish asbestoslike material (table 3). Analysis of the supernatant solution showed that a fraction poor in hydroxyproline and sugar was dissolved.

DISCUSSION

Bovine residual protein was treated with various enzymes in attempts to remove by selective hydrolysis either a possible noncollagenous glycoprotein or a polysaccharide (table 4).

A single treatment with trypsin effects a weight loss of about 20 percent of the original residual protein preparation. The remaining protein is enriched in collagen as evidenced by the increased percentage of hydroxyproline. The material solubilized by trypsin was low in hydroxyproline content, indicating that it is not a collagen. Two explanations are possible: this may be a protein which contains about 4.5 percent hydroxyproline, or more likely, another protein is dissolved along with a small amount of collagen. Analysis of both the protein remaining after repeated trypsin treatments and the supernatant solutions shows a relative enrichment of the sugar component. It is of interest that little free proline or hydroxyproline were produced by the action of trypsin. These amino acids are split off within large polypeptide units.

TABLE 2

COMPOSITION OF SUPERNATANT SOLUTION FOLLOWING TRYPSIN HYDROLYSES OF SAMPLE 4

Number of Trypsin Treatments	Hydroxyproline, % of Weight Solubilized	Sugars, % of Weight Solubilized	Sugar/HO-Pro.
1	4.7	4.2	0.89
2	7.5	6.1	0.81
3	6.6	3.9	0.59

TABLE 3

EFFECT OF ELASTASE ON RESIDUAL PROTEIN

	% Weight	% Nitrogen	% HO-Pro	% Sugar
Elastase Solubilized	37		2.6	1.6
Residue after Elastase	63	14.5	13.4	7.1
Starting Residual Protein (Calc.)	100		9.5	5.1

TABLE 4

COMPOSITION OF RESIDUES AFTER ENZYME TREATMENT

Enzyme Used	% Wt. loss	% Nitrogen	% HO-Pro	% Sugar	HO-Pro / N	Sugars/N
Trypsin, from Table 1 (averages)	20	14.4	12.6	6.0	0.87	0.42
Chymotrypsin	23	16.0	14.1	5.9	0.88	0.37
Carboxypeptidase	7	15.1	14.1	6.2	0.94	0.41
Emulsin	24	14.9	13.8	6.1	0.93	0.41
Collagenase Cl. histolyticum	93		13.5*	4.7*		
Elastase	37	14.5	13.4	7.1	0.92	0.49

* % wt. material dissolved.

Chymotrypsin had about the same effect on residual protein as trypsin.

Emulsin brought about a sizable weight loss, but the percentage of sugar in the solubilized material was lower than it was in the material resistant to emulsin.

Elastase reduced the weight of insoluble protein by about one third. The slight amounts of hydroxyproline and sugars removed suggest that this enzyme preferentially removed noncollagenous material and that the sugar is quite firmly associated with the collagenlike protein.

Both collagenases dissolved our residual protein preparations, the difference in rate depending upon their relative activities. Essentially all of the hydroxyproline was split off in the form of nondialyzable polypeptides.

The insoluble vitreous residual protein appears to be composed of about two thirds of a collagenlike protein firmly linked to carbohydrate (glucose and galactose) and one third of a protein susceptible to solubilization by a variety of enzymes.

Typical collagens have about 17 percent nitrogen whereas our usual starting material is never brought to more than 14 to 15 percent nitrogen. Since the sugars are finely bonded to the collagen throughout these various enzymatic treatments as well as the solubility experiments* they appear to be integral with it rather than to function as interfibrillary cement.

SUMMARY

1. The insoluble residual protein of bovine vitreous appears to be a mixture, two thirds of which is a collagen-sugar compound.

2. The sugars stay with the collagen during treatments with various enzymes and are probably a firm part of the protein molecule rather than interfibrillary cement.

3. The enzymes collagenase and trypsin split the residual protein mainly into large proline and hydroxyproline containing polypeptides although eight to 10 other amino acids or peptides can be found on chromatograms prior to acid hydrolysis.

Francis I. Proctor Foundation (22).

* See preceding paper, pages 228-231.

REFERENCES

1. Bembridge, B. A., Crawford, G. N. C., and Pirie, A.: Brit. J. Ophth., **36**:131, 1952.
2. Grignolo, A.: Arch. Ophth., **47**:760, 1952.
3. Schwartz, W. Z., and Schuchardt, E.: Ztschr. Zellforsch., **35**:293, 1951.
4. Schwartz, W. Z.: Ztschr. Zellforsch, **36**:284, 1951.
5. Gross, J., Matolsty, A. G., and Cohen, C.: J. Biophys. & Biochem. Cytol., **1**:215, 1955.
6. Sugiura, S.: Acta Soc. Ophth. Japan, **58**:1119, 1954. Cited in Am. J. Ophth., **39**:124, 1955.
7. Matolsty, A. G., Gross, J., and Grignolo, A.: Proc. Soc. Exper. Biol. & Med., **76**:857, 1951.
8. Schwartz, W.: Ztschr. Zellforsch., **36**:45, 1951.
9. Suran, A. A., and McEwen, W. K.: Am. J. Ophth., **42**:338 (Oct. Pt. II) 1956.
10. Dische, Z., and Zelmanes, G.: Arch. Ophth., **54**:528, 1955.

11. Neuman, R. E., and Tytell, A. A.: Proc. Soc. Exper. Biol. & Med., **73**:409, 1950.
12. Pirie, A., and Van Heyningen, R.: Biochemistry of the Eye. Springfield, Ill., Thomas, 1956, p. 247
13. Konno, K., and Altman, K. I.: Nature, **181**:994, 1958.
14. Gilbert, J. B., Price, V. E., and Greenstein, J. P.: J. Biophy. Chem., **180**:473, 1949.
15. McEwen, W. K., and Suran, A. A.: Am. J. Ophth., **50**:228-231 (Aug.) 1960.

MODERN THERAPY OF UVEITIS*

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The ideal management of uveitis would combine identification and eradication of the etiologic agent or mechanism with immediate treatment of the inflammation. This would involve establishing the etiology and developing a specific therapy. Most of the literature assumes that uveitis is instigated by bacterial, viral, or parasitic infection which must be treated to cure the disease or prevent its recurrence. It is an unfortunate fact that the etiology of uveitis is discovered frequently in the literature but rarely in the patient.

There are many causes for uveitis. Most cases are probably due to an allergic reaction to various organisms. The etiology is occasionally determined, usually in patients whose systemic symptoms are such that the etiology is obvious. My contention is that we have become bogged down in a traditional, usually unrevealing, survey-type of approach to intraocular inflammation. It is a common error to assume that any positive finding in the survey must be the cause of the uveitis. As a rule this makes for erroneous thinking and at times erroneous therapy. In the meantime, therapy which might have saved the eyes is withheld. If the lesion is overwhelming or in the macula, the time wasted awaiting the results of this survey will provide an opportunity for more havoc to be wrought within the eye. Many a patient still winds up with his sinuses routinely exenterated or his teeth extracted, thus leaving his skull devoid of almost everything save the uveitis. Many ophthalmologists agree with this point of view and volunteer the fact that they have almost never found the cause of uveitis in their practices. Nevertheless, etiologic survey is still the vogue because the literature indicates that it should be.

In all fairness, it must be stated that those ophthalmologists who are especially interested in uveitis are not happy about the present management of this disease, nor the concepts which many of them have advanced for its pathogenesis. While many of their written statements must, of necessity, sound dogmatic, their thoughts are not in the same category.

We need a fresh approach to the problem of etiology of uveitis. At the same time, I must confess that I do not have that new approach. This does not mean that these eyes cannot be saved. They usually can be, with nonspecific steroid therapy.

Realism and the patient's welfare would dictate that the practicing ophthalmologist should immediately institute corticosteroid therapy when the diagnosis of uveitis is made. He should leave the development of better methods of identification to the laboratory research worker until such a time as a practical, efficient clinical method of pinpointing etiology has been developed. There are few patients who would be excepted from this rule.

Too many ophthalmologists have become so bogged down in discussions of the mishaps which took place during the learning period of corticosteroid therapy, that they

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* From the Department of Ophthalmology, New York Hospital-Cornell Medical Center and The L. Margolyes League. Presented before the Chicago Ophthalmological Society, December, 1958.

have forgotten that any treatment is only as good as the physician's skill in its use.

This discussion will limit itself mostly to those forms of endogenous uveitis[1,2] seen commonly in this country, and not to the few rarities caused by such conditions as amebae, fungi, trypanosomiasis, and so forth.

Corticosteroid therapy is the guest who came to visit arthritis and remained for dinner with ophthalmology. The full significance of this has escaped many ophthalmologists, including some who are considered experts in this field. Most patients with serious eye disease are otherwise healthy; whereas, most of those with arthritis, for example, generally have unhealthy tissues. This may account for the paucity of serious side-effects in well-managed systemically treated ophthalmic patients.

Indications and Contraindications

Emotional bias is not a contraindication to the use of steroid therapy. The indications and contraindications should be based upon available facts and not upon a philosophic or library research type approach to therapy. The indications are symptomatic—inflammation, allergy, edema, granulation tissue, and certain infections (concomitant antimicrobial therapy mandatory). The chief ocular contraindications are herpes simplex and fungal keratitis. Truman Davis[3] has recently reported a proven case of exogenous fungus uveitis without keratitis which was controlled only by steroids, until the mycelia were removed.

Nielsen[4] and Kirby have published a comprehensive survey of the various methods of managing specific types of uveitis. Woods'[1] incomparable volume, *Endogenous Uveitis*, should be required reading for all practicing ophthalmologists. These publications serve as excellent résumés of the various forms of specific therapy employed in uveitis; summarized in Table 2. Braley[5] has recently called attention to amebiasis as a cause of a central lesion simulating central serous retinopathy or central choroiditis. In his experience, patients with this condition did poorly on systemic steroid therapy and did well on an appropriate anti-amebic regime.

Etiology

The current etiologic trend is still in the direction of toxoplasmosis, which may well be the most important cause of chorioretinitis. Here, the therapeutic regimen closest to a specific is the use of pyrimethamine plus sulfadiazine. Pyrimethamine must be used at a high dosage level to be effective; the first days' dose should be 200 mg., decreased to 75 mg. the second day. Thereafter, at least 50 mg. should be given daily along with sulfadiazine (1.0 gm., four times daily). Foleinic acid may neutralize the toxic tendencies of the pyrimethamine.

Cases presumed to be due to toxoplasmosis frequently do well on systemic corticosteroid therapy. The aim of the chemotherapy is destruction[7] of the organisms and prevention of recurrences. The necessary high dosage level of pyrimethamine and sulfonamides constitutes a toxic therapy whose complications usually appear to be reversible upon discontinuance of therapy. Nevertheless, if this regimen is indicated, it should be employed, but the blood picture should be carefully watched. It is conceivable that this regime may be more effective in acute than in chronic infection, and concomitant steroids would appear to be a rational approach. Toxoplasmosis acts differently in the infant than in the adult. In the former, corticosteroid therapy may be deleterious; in the latter, it is often beneficial. Histoplasmosis is now being emphasized as etiologic in uveitis.

Tuberculosis has been the chief target of uveitis-conscious ophthalmologists for years. In evaluating my experiences with uveitis, especially choroiditis, I must conclude that human uveal tuberculosis has either become a rarity or is influenced beneficially by corticosteroid therapy. Many studies have reported[6–10] excellent results in treating pulmonary tuberculosis with a combination of chemotherapy and steroids. Certainly, if one

feels strongly that he is dealing with a presumptive case of ocular tuberculosis, this combination is indicated.

If one is familiar with the well-conducted studies of pulmonary tuberculosis, the rationale for combined steroid-antimicrobial therapy of this and other granulomatous diseases becomes obvious. There are several facts which are important in this respect. Steroid therapy does not affect fibrosis which is already present but it does prevent active fibrosis from taking place. Therefore, this therapy would not affect an already formed tubercle, sarcoid lesion, or choroidal scar. In adequate doses, it should prevent the formation of new tubercles or cavities, while the concomitant antimicrobials attack the organisms. The response of the disease is[10] "probably in proportion to how fresh and cellular the disease is in contrast to its being old and fibrotic." When the disease is fresh, it is much more likely to be responsive.

The work of Margaret Smith[8] and others in childhood tuberculosis and tuberculous meningitis serves to prove these ideas further. An important aim of this regimen is to prevent the rebound phenomenon which was produced in some of the animal work with steroids and antimicrobials in the treatment of experimentally produced ocular tuberculosis.

It is the[7] anti-inflammatory and anti-allergic effects of the corticosteroids that make them valuable in acute infectious diseases where, after all, the overwhelming inflammation causes as much damage as the infection itself. Nowhere is this more true than in the acute inflammatory state of tuberculosis, where the blockage of blood vessels and the subsequent damage of the lung produce as much destruction as the toxic effect of the tubercle bacillus. The use of corticosteroids at this stage, not waiting until the cavity is well developed, seems to inhibit this tremendous amount of inflammation which is largely an allergic response, thereby aiding the rapid action of the effective antimicrobial drugs.

It is worth noting that in the early as well as in the late stages of tuberculosis, the pathology itself is almost avascular because of the inflammatory effect. Therefore the ability of the antimicrobial drug to reach the area of actual infection is interfered with by the inflammatory and allergic reaction of the tissue to the tubercle bacillus. It is in such instances that the use of corticosteroids is particularly effective.

These statements plus my own experiences constitute the reasons for disagreeing with those ophthalmologists who feel that steroid therapy is contraindicated in granulomatous uveitis.

Woods states: "In granulomatous uveitis,[3] adrenal hormonal therapy has at best only very limited usefulness, and usually is specifically contraindicated." His statement is based mainly on animal experiments in which cessation of therapy produced a rebound phenomenon, while the steroids had prevented encapsulation of the organisms. He further states that: "There are innumerable clinical observations of the deleterious effect of prolonged hormonal therapy on granulomatous uveitis."

Recently I reviewed a series of 93 patients with chronic uveitis, who had been treated for periods varying from three months to nine or more years. Twenty-three of these patients were dependent upon the involved eye because of blindness, central scarring, or absence of the contralateral globe. Seventy-nine of this group were considered as controlled or as having achieved a biologic cure. Six were considered as unchanged or "equivocal" and eight as failures. Most of the failures occurred in patients whose therapy was discontinued abruptly while at a high level of dosage, thus permitting a rebound to occur. Many of this group, including a number treated for years with steroid therapy, fall into the category of cases of granulomatous uveitis. Many other such patients have been seen in consultation. It has been my experience that many granulomatous patients are treated successfully on steroids, only to fail because the ophthalmologist becomes frightened about prolonged steroid therapy, even when no important side-effects intervene.

The Research Committee of the Tuberculosis Society of Scotland found prednisolone plus chemotherapy beneficial in tuberculosis, most of the significant improvement occurring in the first two months. No one of the series of 46 patients treated over a period of 18 months (as compared to a control group of 48 patients treated with chemotherapy

alone) showed evidence of deterioration. A temporary rebound was observed radiologically in 17 percent. "The authors make it clear that corticosteroid therapy in tuberculosis is fraught with danger unless covered by adequate specific chemotherapy, but that there is no risk if this is given." In the acutely ill patients, there was evidence that prednisolone reduced the toxic effects of tuberculosis.

Woods[1] has indicted the streptococci as a frequent cause of nongranulomatous uveitis. Coles and Nathaniel[11] and Hallett, et al.,[12] have failed to confirm this in their studies of streptococcal serology.

Franchescetti[13] has suggested that macular lesions are frequently due to infections of the teeth and sinuses; juxtapapillary lesions are usually tubercular; and disseminated lesions are evidence of chronicity and are probably due to bacterial infection. I disagree with these observations. It is my impression that most uveitis is due to an allergic reaction rather than to a specific infection. It is possible that uveitis is a result of a vascular reaction to infection elsewhere. Many patients have been seen who have had sufficient previous treatment with antibiotics to make one expect any locus of infection to have been sterilized. Nevertheless, the uveitis has continued unabated. Perhaps once the uveitic reaction has been initiated, it sets up an allergic reaction which continues on its own. The good responses to steroid therapy may be evidence of the allergic nature of uveitis.

Clinical course (fig. 1)

What happens if the uveitis is untreated or is inadequately treated with steroids? All ophthalmologists have seen patients who deny any antecedent eye diseases but who, nevertheless, exhibit undeniable evidences of old synechias, iris pigment on the lens surfaces, or healed choroidal lesions. Undoubtedly, occasional cases will heal spontaneously but the physician who relies on such cure is gambling with his patient's eye. An untreated anterior uveitis with an exudative predilection will terminate with anterior and posterior synechias, which may result in a secondary glaucoma.

When a severe uveitis, especially choroiditis, is treated inadequately, for example with one quarter or one third of the adequate daily dose, the steroid often seems to feed the fury of the inflammation. In a really "hot" uveitis, no steroids are better than a little.

Some cases of anterior uveitis will retain a central area of endothelial bronzing, even when adequately treated. This may also follow a glaucomatocyclitic crisis.

A long-continued posterior uveitis eventually causes posterior subcapsular cataracts. Many cases exhibit vitreous detachments, bands, and membranes. Gross cystic changes

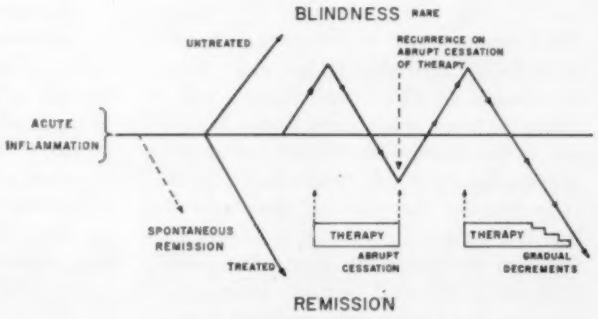

Fig. 1 (Gordon). This chart depicts the management of acute intraocular inflammation. The horizontal line is the baseline. The diagonal line represents an acute disease. If untreated, the disease may go on to blindness or it may recover spontaneously. If treated adequately, it should respond. If treatment is discontinued too abruptly, it may relapse. In the latter eventuality, treatment is resumed and later tapered off by steplike decrements every several days. As long as there is no relapse, the tapering off process continues until zero is reached. Relapse is a signal for increasing the dose.

in the macula and elsewhere in the retina are infrequent but serious complications.

The retinal vessels in the eye with uveitis which is untreated or inadequately treated will exhibit venous engorgement and a marked increase in the width of the arterial reflex stripes but with a concomitant decrease in the highlight and visibility of those stripes, so that the arteries present a "thin-walled" appearance. There may even be a uveitis-induced arteriosclerosis not noted in the uninvolved eye.

An occasional case will exhibit a dense, white solid-looking elevated area, usually below, resembling Coats' disease. This probably represents a solid detachment. Apparently an aphakic eye can withstand a long-continued aqueous beam without grossly demonstrable clinical damage. This same "fire" apparently will cause and has caused the cataract during the phakic stage. Iris atrophy is common and at times iris neovascularization is seen.

The most resistant forms of uveitis are those that affect the choroid:

The first is that type in which a huge, elevated, virtually a choroidal "abscess," involves practically the entire superior or inferior quadrant. These cases may respond to systemic steroids but only after a long interval of sustained, intensive therapy.

A second group, which paradoxically enough often exhibits little or no evidence of inflammation, comprises a host of conditions of dubious nomenclature. They may resemble choroiditis—frequently of the disseminated variety. One sees cases with new lesions, often without any surrounding edema or other evidences of activity, but with a history of "flashes of light" and disturbances of vision; at times small hemorrhages are present in the retina. The central serous retinopathies belong in this "waste basket group." It is doubtful that most of them represent true inflammatory reactions. A missed small temporal juxtapupillary lesion can be easily mislabelled "central serous retinopathy." Juxtapapillary lesions are resistant to treatment. The initial response to therapy is good but the last few degrees of "cure" take a long time. Subconjunctival (subtenon's) injections of steroids are helpful.

It is sometimes difficult to be certain whether activity is present. The more important signs and symptoms of activity are aqueous beam and cells, vitreous cells, lightning flashes, sudden occurrences of spots usually in "clouds," hypopyon, retinal hemorrhage, wet keratic precipitates or fine endothelial edema (bedewing), softness or fluffiness of the choroidal lesion, edema of the retina or nervehead, engorgement of the veins, the arterial changes already noted, an increase in intraocular pressure, and decrease in vision.

Clinically, I have seen no reason to believe that corticosteroid therapy affects vitreous or retinal hemorrhages, either beneficially or adversely. If there is any reason to believe that the vitreous hemorrhage is associated with an active choroiditis (and this is not uncommon), systemic steroids should be employed in an attempt to control the choroiditis.

Management

The modern approach to the treatment of uveitis combines immediate management of the inflammation with corticosteroid therapy, supplemented or replaced by specific therapy in those cases where the etiology is known or obvious, and where such specific therapy exists.

This treatment of acute or recurrent uveitis is usually satisfactory even though it does not attack the cause of the disease. The therapy of chronic uveitis is an admittedly stop-gap procedure but, when administered properly, the eye can be kept relatively intact until some better form of management is discovered. The specific regimen is dependent upon the site of involvement in the uveal tract, upon the chronicity of the disease, and upon one's knowledge of the patient's physical status.

Acute and recurrent anterior uveitis

Anterior uveitis includes iritis and cyclitis. If seen early, most cases will respond to repeated frequent topical applications with any of the preparations listed in Table 1. Ointments are more effective than drops over a long period of time. However, they create a film which blurs vision and hence should be reserved for night time use, unless vision is already so poor that the film will not be additionally disabling. Initially, the drops should be used every half hour to every hour, the interval being lengthened as the condition responds.

At the first visit, the eye should be dilated with one of the shorter-acting cycloplegics, such as Cyclopentolate or homatropine to permit a thorough examination of the fundus. Such an examination rules out such other conditions as choroiditis, neoplasms, retinal detachments, vitreous hemorrhages, and so forth, which can cause aqueous flare and cells. At the same time, fresh anterior synechias will usually be broken.

It does not seem necessary to utilize cycloplegics further in anterior uveitis unless those adhesions present are not broken by the original dilatation. Corticosteroid therapy has a lytic and preventative action on adhesion formation. There is no point to needless interference with stereopsis by continuous dilatation of a pupil which exhibits no or old fibrotic, unbreakable synechias, if adequate steroid therapy is employed and if the patient is under reasonable observation. This statement is based on over nine years of experience.

It would be valuable to have some index by which to evaluate the probable therapeutic response of a specific lesion and to differentiate between a response to medication and a spontaneous remission. Because this is impossible and in view of the demonstrated

TABLE 1

Available systemic preparations*

Agent	Initial Dosage
Cortisone	300–200 mg.
Hydrocortisone	160–120 mg.
Prednisone-Prednisolone	30– 40 mg.
6-Methyl prednisolone	24– 32 mg.
Triamicinolone	24– 32 mg.
Dexamethasone	3.0–4.5 mg.
Corticotropin	80–120 units i.m.; 25 units in 1,000 cc. saline IV

* All of these, excepting corticotropin and additionally including 9 alpha fluorohydrocortisone are potent topically. Cortisone and hydrocortisone are rapidly being replaced by newer products.

TABLE 2

Specific therapy

Blastomycosis, Cryptococcus, Histoplasmosis—
- Nystatin (1.5 million units daily) = (questionable value)
- Ethylvanillate 15–30 gm.—daily—slowly
- Increased to 45 gm. for 6–7 weeks (toxic)
- Amphotericin B—probably best today

Onchocerciasis—
- Surmin sodium (antrypol)
- GMI—per week (X6–7) or diethylcarbamazine
- Citrate (Hetrason) 35–140 mg.—3Xweek for several weeks

Gonococcus—
- Penicillin—sulfanomides.

Amebae—
- Diiodohydroxyquin 615 mg. t.i.d.
- Chloroquine 0.5 gm. QHS
- Carbarsone 0.25 gm. t.i.d.

Fungi—
- Nystatin
- Attempt desensitization
- Griseofulvin
- Amphotericin B

Leptospirosis—
- No known effective therapy

Virus—
- No effective therapy
- Sulfonamides and chloramphenicol or chlortetracycline against large viruses, adenovirus vaccine

TABLE 2A

Specific therapy

Syphilis—
- Chemotherapy, usually with penicillin

Tuberculosis—
- Chemotherapy with the streptomycins, isonicotinic acid hydraside, paramino-salicylic acid and the newer agents with or without steroids. These have replaced desensitization

Brucellosis—
- Foshay vaccine
- Chlortetracycline with dihydrostreptomycin

Toxoplasmosis—
- Pyrimethamine (Daraprim) plus sulfonamides (sulfadiazine)

Trypanosomiasis—
- Intravenous arsenicals

Actinomycosis—
- Penicillin plus potassium iodide (value is questionable)

TABLE 3

REASONS FOR FAILURE OF STEROID THERAPY

1. Wrong route of application
2. Too little, too late
3. Too short a course of therapy
4. Failure to switch to an alternate compound after a fair trial at a presumably adequate dosage level
5. Lack of specific therapy
6. Using steroids in presence of ocular contraindications
7. Abrupt cessation of therapy, producing a rebound

efficiency of systemic therapy with either corticotropin (ACTH) or the adrenocortical steroid hormones, I treat virtually every case of anterior uveitis with such systemic therapy from the onset. While such cases might have done well on topical medication alone, their courses have been shortened by the addition of the systemic therapy. Usually a markedly beneficial response is evident within 96 hours.

If an improvement is not noted by this time, one must now ask himself, "Am I using the right preparation for this particular patient, and if so, am I using enough of it?" Though most patients will respond equally well to either corticotropin (ACTH) or to one of the corticosteroids, there are some in whom one of the available preparations will function better than the others. There is some relationship between the severity of the disease and the amount of drug which is needed to control it. Since one cannot gauge accurately the power of the disease which he is opposing, it is wise to begin with large initial doses.

New synthetic adrenal corticosteroids are pouring out of the laboratories with such rapidity that one can no longer speak precisely unless he discusses experiences with a specific drug, since each patient may be affected differently by different steroids. All attempts are in the direction of a highly anti-inflammatory preparation which will produce no adverse side-effects. Up to this moment, and that includes dexamethasone, which is a most potent agent, the ideal has yet to be achieved.

The ophthalmologist who is reluctant to employ corticosteroid therapy because of lack of experience should obtain immediately the services of someone more competent in this field, especially if the patient's only eye is involved. Some time ago I sent out a questionnaire on therapy. In a covering letter, one respondent stated that he had had two patients go blind with uveitis that year. Then, in the questionnaire proper, he stated that he had never used corticosteroid therapy because he "had never had a patient who needed it."

Initially, 80 to 120 units of a long-acting form of corticotropin (gel or zinc) are employed in single injections or in two divided injections 12 hours apart; or equivalent amounts of an oral corticosteroid (table 1) are given in divided doses daily. In the average case of intraocular inflammation, an initial recommended daily dose is six tablets of the 0.5 mg. (or four tablets of the 0.75 mg.) of dexamethasone or six of the 4.0 mg. of 6-methyl-prednisolone or triamcinolone, or their equivalents in other steroids or ACTH.

If the disease appears severe, start with 30 to 50 percent greater doses. For convenience, it is easier to speak in terms of "tablets" than to state repetitiously the dosage of all of the steroids. In short courses of systemic therapy lasting a week or two, the problems of water retention, tapering, and so forth are unimportant as a rule. Therapy is continued at the same level as the initial dose and can be terminated abruptly if the course has lasted less than two weeks. If steroid therapy is employed for longer periods, dosage should be tapered off by decrements of one full tablet per day, or its equivalent. Otherwise, the disease may rebound with even greater intensity than the original inflammation. When the amount given in acute uveitis is at a fairly high level and a good response has not been noted within several days, one of three courses should be considered: (1) increase the dose, (2) switch to an alternate preparation of steroid or to ACTH, (3) add subconjunctival injections of steroids.

If the acute process is resistant, as it

frequently is, it must be treated for as many weeks or months at a high dosage level as are necessary to obtain an excellent result. If, for example, a patient has been on 3.0 mg. of dexamethasone for six weeks with a marked decrease in the aqueous beam and cells from four- plus to two-plus (an obvious improvement), it is not necessary to wait for abolition of the anterior chamber signs to decrease the initial dosage. The amount given can be decreased now by decrements of one-half to one tablet every three or four days. The patient's status should be reviewed frequently. One should never be in a hurry to decrease the dose rapidly when the patient is doing well.

Topical steroids should be employed concurrently and should be continued for an additional two weeks or so after systemic therapy has been discontinued. If the patient is on corticotropin (ACTH), a similar plan of decreasing by steplike decrement of 10 units should be used. When the patient has been on parenteral steroids for a period of three months or more, it is advisable occasionally to substitute two weeks of ambulatory intramuscular ACTH to prevent adrenal atrophy. If a patient who is on, or has been on, systemic corticosteroids within the past two or three months, suffers a medical or surgical emergency, the steroids must be continued or restarted. The dose employed should be the equivalent of six tablets initially, tapering off slowly.

Systemic corticosteroid therapy by any but the intravenous route is an ambulatory procedure. Most cases of anterior uveitis, including those which are severe, do not require hospitalization. When the amount is being decreased, any recurrence in the intensity of inflammation should be a signal to increase the dose immediately by approximately 25 percent.

Therapy at an adequate level must be continued until the case is brought to a successful conclusion. The only excuse for discontinuing treatment is cure or the onset of severe side-effects. Side-effects are rare; their managment will be discussed later. The physician must never place an arbitrary time limit on the number of days of therapy which he will "give —or else."

In my opinion an etiologic workup is of no value in the treatment of the average case of acute anterior uveitis, unless the cause is grossly obvious or the case proves unusually

TABLE 4

GUIDING PRINCIPLES IN CORTICOSTEROID THERAPY

1. Use enough—soon enough—often enough—and long enough to obtain the desired results
2. Suppress the inflammation, and keep it suppressed until it burns out. Ascertain the minimum necessary maintenance dose by a process of trial and error. Constantly attempt to decrease by steplike decrements. This reduction is continued if no relapse occurs. Increase immediately on reappearnce of signs and symptoms of the inflammation
3. In therapy longer than two weeks, never stop abruptly at a high dosage level or a serious rebound may occur. If stoppage is mandatory use subconjunctival depot injections and attempt rapid tapering
4. Systemic contraindications do not apply to the use of topical or subconjunctival routes
5. The reaction of a specific ocular entity may vary depending upon whether the route of administration is topical or systemic
6. Failure of one steroid is not to be construed as meaning that the other available steroids will fail also
7. Most failures are due to insufficient doses
8. One should never start with the presumption that a case is hopeless
9. Corticosteroid therapy is not to be regarded as 12th hour therapy, but should be instituted immediately on indication
10. "Too little" may be worse than "no steroids" at all

resistant to high dosages of systemic corticosteroid therapy.

Acute choroiditis and posterior uveitis

Inflammations of the uveal tract behind the ciliary body are not affected by topically applied steroids and require systemic and/or subconjunctival therapy. The program is similar to that outlined for the systemic therapy of anterior uveitis. The disease must be treated intensively; the closer to the macula the lesion, the more urgent and intense the therapy.

These patients are given an immediate (subtenon) injection of steroids plus 120 to 160 units of long-acting ACTH intramuscularly. This is followed by the initiation of either long-acting corticotropin in daily doses to 120 to 160 units or intravenous infusions of corticotropin until satisfactory response has been obtained, or by oral steroids at a level of eight to 12 tablets daily.

If the patient is suffering from macular choroiditis in his only eye, he should be admitted instantly for intravenous corticotropin after first receiving the subtenon and intramuscular injections of steroids and corticotropin in the office. When administering corticotropin intravenously, use 25 units in 1,000 cc. of saline regulated to 20 drops a minute and allowed to run from 12 to (preferably) 16 hours. The arm is affixed to a short padded board, thus permitting the patient ambulation within the hospital. The drip is continued for as many days as are necessary to obtain a marked improvement.

Following this the patient can be discharged from the hospital on either intramuscular ACTH, approximately 80 units daily at first, or on corticosteroids, approximately six to eight tablets initially in divided daily doses. The dose is decreased slowly as the condition improves. Most patients can be continued on surprisingly high levels of systemic steroids for long periods without obvious side-effects. Subconjunctival injections of steroids administered every seven to 14 days as indicated by the progress of the disease are often effective, either as adjuncts or as the sole therapy.

Therapy is continued until the lesion becomes hard and white, with or without pigmentation. Only then can medication be safely tapered off, and then preferably over several weeks' time. If the lesion is yellow and soft and otherwise apparently inactive in appearance, it will relapse if dosage is decreased too abruptly. A diminution in caliber of the dilated retinal vessels and decreases in the retinal edema are other signs pointing to healing. Systemic therapy should never be abruptly terminated. If such a decrease is deemed mandatory, subconjunctival therapy should be substituted immediately.

Recurrent uveitis

Since each additional attack is damaging, treatment must be instituted promptly upon a recurrence. The etiologic survey can be conducted simultaneously with the corticosteroid therapy if one so desires. The specific therapy then indicated should be employed, if any is available. Unfortunately, the survey is usually fruitless. Corticosteroid therapy is not indicated in the free intervals between recurrences.

Chronic uveitis

In a case of chronic uveitis in which no specific therapy is available, the physician is faced with the probability of having to continue for months to years medication which will undoubtedly produce a certain amount of water retention and possibly other side-effects. The only alternative may be blindness. The more important side-effects are gastrointestinal ulcers and psychoses. These can be guarded against by watching the patient's mental behavior and by being alert to relevant complaints. Patients who are psychotic or who have histories of gastrointestinal ulcer have been successfully treated with systemic corticosteroid therapy. Fortunately, complications are rare in alert hands.

The regimen here is an extension of that

utilized in the treatment of acute and recurrent intraocular inflammations. A thorough search for the etiology is justified, although usually unrevealing. If clues are obtained, they should be followed. The chief aim in the treatment of the chronic case is to formulate a program which will subdue the inflammation rapidly while safeguarding the patient's general welfare.

One should attempt to keep the inflammation suppressed with a treatment schedule, as determined by a method of trial and error, which will enable the patient to be ambulatory (fig. 2). The amount of vision which can be restored to a badly damaged eye is often considerable, and is dependent upon the amount of vitreous and macular damage. This cannot be estimated until after an initial period of treatment. As a rule, the chronically diseased eye will require at least several weeks of intensive systemic therapy before much response can be anticipated. In severe cases the patient may be hospitalized on intravenous corticotropin or large doses of systemic corticosteroids, initially. The goal of continued suppression of the chronic symptoms can be realized frequently by careful juggling of the available compounds and routes of usage. Remissions may occur. If the globe has been kept relatively intact, the patient benefits, and the ophthalmologist gains a welcome respite.

If systemic therapy is employed and only one eye is affected, the dose must be adequate to control that inflammation. If two potentially useful eyes are involved, the amount of medication must control the disease in both eyes. If both eyes are involved, and one is obviously hopelessly blind, only the amount necessary to control the inflammation in the useful eye should be used. If both eyes are involved and one is useless, due to a cataract or some other cause which can eventually be remedied, the inflammation in both eyes should be controlled. If both eyes are essentially phthisical, treatment is hopeless. But when both eyes (or the only remaining eye) are involved and not completely destroyed, the physician should gamble with all at his command in a desperate effort to salvage something from the wreck.

Neilsen and Kirby[4] state that steroid therapy is contraindicated in Behçet's syndrome. This statement is based on reports by Sezer[14] and France, Buchanan, Wilson, and Sheldon.[15] I have had only one proved case of Behçet's syndrome and this case has been controlled with large doses of ACTH (120 to

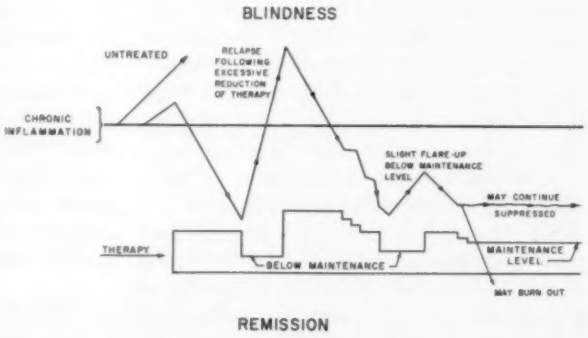

Fig. 2 (Gordon). This illustrates the management of chronic intraocular inflammation. The course of the disease without treatment is often progression to blindness. If adequate treatment is instituted, the disease usually responds. Once a good response is obtained, the dose is dropped. If the decrease in dosage is too great, a relapse occurs. At this point, therapy must be increased at a higher level than at the time of relapse, and maintained until a beneficial response is obtained. Then, dosage is slowly tapered off by decrements of one tablet of oral steroids (or 10 units of ACTH), decreasing the amount every week or two until the minimum dose is found which will keep the disease suppressed. In true chronic uveitis, it is rare to be able to discontinue therapy completely.

200 units daily) for almost two years; more recently dexamethasone (4.0 to 5.0 mg. daily) has been used. This man was eventually hospitalized in his home state and the steroids discontinued abruptly. There was a severe rebound with ultimate blindness. This one case does not prove a point but only supports the contention that many statements regarding the contraindications or failures of corticosteroid therapy are due to incomplete dosage levels or to library-type research.

For the purpose of corticosteroid therapy, division into granulomatous or nongranulomatous uveitis is unnecessary. Nor should any case be considered hopeless in advance of trial therapy. If a fair trial on intensive systemic steroid therapy fails to benefit the uveitis, one could empirically give a four to six-week course of an antitoxoplasmosis or antitubercular regime, or both successively if necessary. An antihistoplasmosis regimen might also be in order.

Management of side-effects

In long-term therapy, it is well to guard against water retention and potassium loss by ordering potassium chloride (4.0 gm. daily) and by restricting fluid and salt intake. When mooning of the face or other signs of water retention are observed, 500 mg. of chlorothiazide are given every other day, daily, or more often if necessary. The mercurial diuretics can also be employed, preferably intramuscularly or orally. At times, one tablet of chlorothiazide or one of the carbonic anhydrase inhibitors or an injection of mercury will cause as much as three to five pounds of water loss in one day. Often, the oral diuretics will be effective at first, only to lose their potency later. In these cases, deep intramuscular injections of 2.0 cc. of mercuhydrin sodium are effective and need rarely be repeated more than once every week or two. Water retention usually is an easy problem to solve. In the presence of secondary glaucoma the carbonic anhydrase inhibitors serve the double purpose of controlling the intraocular pressure and the water retention.

Occasionally, acne will occur during systemic therapy. Topically applied dermatologic preparations of steroids may be effective in combating this condition. Symptoms referable to the gastro-intestinal tract indicate a need for anti-acids or an ulcer regimen. If insomnia or nervousness ensues, sedatives or tranquilizers should be used. In problem cases the services of a medical man trained in steroid therapy are essential.

Subconjunctival injection therapy

Theoretically a potent steroid deposited under tenon's capsule should constitute ideal depot therapy, providing a constant source of anti-inflammatory medication with no concomitant systemic effects. In practice, however, the depot injections do not fulfill these expectations in a sufficient number of cases to justify reliance upon them as the sole source of corticosteroid therapy. Suspensions of steroids will function as depots longer than solutions. Attempt to give every subconjunctival injection high up under the upper lid regardless of the number of previous injections. The interval between injections varies from seven to 10 days; however, when they are the sole method of treatment, they may be required more often.

If more powerful mydriasis is desired, one to two drops of sterile atropine or other mydriatic can be added in the same syringe. Hot compresses for the next day or two relieve the edema and discomfort. If there is any contraindication to systemic therapy, such as gastrointestinal ulcers, the subconjunctival route may be imperative if the eye is to be saved. Some of my patients have had from 20 to 50 or more such injections without any observable ill-effects. Many with apparent contraindications to systemic therapy nevertheless tolerate systemic treatment, especially with proper medical management.

Depot and intravenous steroids

Corticosteroids are now available in both depot intramuscular and rapid intravenous forms. I have had over four years' experience with the intramuscular use of depot

(long-acting) steroid preparations. With most of these one can assume that approximately five times the daily dose will function as a maintenance dose for one week. Patients usually note fewer side-effects from these than from the daily use of similar preparations. They are especially useful in those patients who cannot be trusted to take the prescribed oral medication, in patients who require systemic medication but have medical contraindications to the necessary dosage, and in the management of acute and chronic intraocular inflammatory conditions. In many early cases of acute uveitis, only one or two such weekly injections, supplemented by the necessary topical steroids, are sufficient to abort the disease.

Theoretically, a rapid intravenous administration of steroids (over a period of several minutes) should be good initial therapy in an acute intraocular inflammation, especially if the macula is involved. In actual practice, this has not proved superior to the management recommended in this paper. Daily intravenous steroids, rapidly injected, have not been as valuable in my hands as the conventional oral route employing the same dosage. The full role of rapid intravenous steroid therapy in ophthalmology still requires delineation.

Sympathetic ophthalmia

While sympathetic ophthalmia cannot properly be termed an endogenous uveitis, it is treated in the same manner as an acute uveitis. One should utilize systemic therapy rather than risk reliance upon topical therapy alone. While some excellent results have been reported with topical therapy, I feel that the diagnosis in some of these cases may have been questionable. Although some cases are relatively mild, the risk is too great to procrastinate by relying on topical therapy.

Role of fever therapy and other adjuncts

Artificially induced fever has played a progressively[4] smaller role since the introduction of the steroids. However, there may still be some patients whose uveitis will respond to fever therapy after failing to respond to an adequate steroid regimen. Where it is effective, fever therapy appears to increase the patient's resistance—a situation which does not characterize the response to steroids. It has the disadvantage of not being a completely ambulatory procedure.

At times intramuscularly injected streptokinase and streptodornase are helpful as adjuncts in the treatment of uveitis, especially in the presence of hypopyon or severe vitreous reaction.[1] On rare occasions phenylbutazone has proved useful, with or without steroids.

Management of complications

Synechias

Synechias, especially when fresh, often melt away under corticosteroid therapy. Cycloplegics or mydriatics should be employed until the synechias have been broken. If they are resistant to topically administered cycloplegics, the "2-2-2" injection, two minims each of atropine, 10-percent phenylephrine or 1:1000 epinephrine plus 4.0-percent cocaine should be employed. Old fibrotic adhesions are unaffected by present therapy.

Myopia

During the active stage of uveitis, the average patient will become more myopic. An occasional patient will come out of an attack with an increase in myopia. The treatment here is proper refraction. Conversely, a central serous retinopathy usually causes a temporary hyperopic effect.

Secondary glaucoma

Secondary glaucoma can be a serious complication, occurring either during the course of uveitis or when it is inactive, with the pupil usually bound down by adhesions. Surgery is rarely necessary except in seclusion of the pupil. Intensive treatment of the active uveitis with adequate corticosteroid therapy, plus the oral use of carbonic anhydrase inhibitors, three to four times daily, will usually make for good control. If the

pressure is controlled for a short period, it will usually remain normal when the carbonic anhydrase inhibitors are discontinued. Failure of the elevated pressure to respond to oral carbonic anhydrase inhibitors indicates a trial with another carbonic anhydrase inhibitor or urea intravenously.

The question of whether to dilate or constrict the pupils always arises. I feel that, if either is to be done, dilatation is preferable, with a trial in the office. Occasionally miotics prove necessary. Paracentesis of the anterior chamber is a good temporizing procedure and may produce a concomitant decrease in the inflammation. When surgery is necessary, it should be done under intensive systemic corticosteroid therapy before, during, and after the procedure. As a rule, peripheral iridectomy is sufficient, unless there are widespread peripheral anterior synechias. The tonometer is a most important tool in uveitis.

Cataracts

Cataracts occur frequently as complications of long-standing uveitis. When surgery is indicated on a patient with active uveitis, he should be placed on adequate systemic corticosteroid therapy before, during, and after the surgery. The dose is the minimal amount which is found adequate to suppress completely the signs and symptoms of inflammation. A subtenon's injection of steroids is given at the time of surgery.

Retinal detachments

Retinal detachment surgery, when required, is done in the same manner as lens extraction, with intensive corticosteroid therapy before, during, and after the surgery if an active uveitis is present. If the uveitis is not active, the detachment may be managed in the same manner as otherwise, without the need for corticosteroid therapy, unless inflammation ensues. In some cases, especially if no tear is found, the detachment is actually an elevated choroidal abscess (in effect) and may respond to the indicated intensive steroid therapy.

Vitreous membranes

Vitreous membranes can often be lysed if long-term steroid therapy or repeated subconjunctival injections are employed. At times the vitreous floaters will melt away. Many weeks of therapy may be required.

Band-shaped keratitis

This can be managed either by the employment of sodium versinate or by the use of two-percent hydrochloric acid.

Optic neuritis

Optic neuritis may occur as part of the uveitis and responds to the systemic therapy. Here corticotropin is often superior to the oral steroids.

Vasculitis or perivasculitis

A mild or severe perivasculitis, usually periarteritis, may occur as an apparently primary entity (at times as part of a polyarteritis), or as a reaction to severe uveitis, usually to a juxtapapillary choroiditis. This demands intensive, early systemic corticosteroid therapy, combined with subconjunctival steroid injection. Vasculitis is always a serious condition. However, in the presence of apparently white and occluded vessels, therapy may often be beneficial, and the white apparently occluded vessels usually prove to have been sheathed vessels which are capable of reverting to nearly normal appearance and function.

Phthisis bulbi

Therapy is useless here.

Discussion and Summary

Corticosteroid therapy is indicated in the management of the uveitides, in the absence of more specific therapy. Its use early enough, frequently enough, and long enough will often prevent considerable ocular damage or even blindness. I believe that the present method of routine survey for etiology has proved unsuccessful because the ability to pinpoint the cause of most cases of uveitis is lacking. In addition, there is very little in

the way of specific therapy. Too often the survey is substituted for therapy; and the eye is permitted to become damaged while treatment is delayed or permanently withheld. "Positive" findings on survey do not necessarily mean that one has discovered the cause of the uveitis. One must differentiate between immediate treatment of a patient and long-term study of a disease process.

Today knowledge of how to handle corticosteroid therapy is essential to the successful management of intraocular inflammations. Corticosteroid therapy is not so much concerned with a new series of drugs as with a new concept. For that reason, one must devote time to acquiring skill in applying these agents if one wishes to give his patients the benefit of modern therapy. An understanding of the pathology of granulomatous uveitis renders the rationale for combined corticosteroid-antimicrobial therapy obvious, and may explain some reported failures.

It must be understood that corticosteroid therapy, employing either the topical preparations or the oral-intramuscular natural and synthetic steroids or corticotropin (ACTH), is symptomatic therapy. The indications are inflammation, edema, allergy, granulation tissue, and certain infections (here concomitant antimicrobials are mandatory). The contraindications are keratitis due to herpes simplex, chickenpox, smallpox, and fungi, as well as the usual systemic contraindications.

The management of acute, recurrent, and chronic uveitis with corticosteroids has been outlined in detail. Rules for guidance and necessary dosage tables, as well as an outline of specific therapies, have been appended.

The fact that a chronic uveitis will relapse upon discontinuing therapy, is not an indictment of that therapy, especially if there is no better alternative. At the same time, long-term steroid therapy is not indicated unless the disease has responded; long-term maintenance therapy is required. Therapy which is ineffective at a high level of dosage for an adequately long trial period should not be continued indefinitely.

After this article was completed, the symposium on uveitis held by the Council for Research in Glaucoma and Allied Diseases, in 1958, was reported.[16] This should be studied by all who are interested in this subject.

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References

1. Woods, A. C.: Endogenous Uveitis. Baltimore, Williams & Wilkins, 1956.
2. Stanworth, A.: The aetiology and treatment of uveitis. Tr. Ophth. Soc. U. Kingdom, **78**:533, 1958.
3. Davis, C. T.: Procedure for removing foreign material. Am. J. Ophth., **45**:569 (Apr. Pt. I) 1958.
4. Nielsen, R. H., and Kirby, T. J.: The modern treatment of uveitis. A.M.A. Arch. Ophth., **58**:79-108 (July) 1957.
5. Braley, A. E., and Hamilton, H. E.: Central serous choroidosis associated with ameplasis. A.M.A. Arch. Ophth., **58**:1-14 (July) 1957.
6. Levine, E. R.: Personal communication.
7. Smith, M.: Personal communication.
8. Riemer, A. D.: Personal communication.
9. Harris, M. S.: Personal communication.
10. Foreign letters (J.A.M.A., p. 184 (Jan.) 1958): Original article in Brit. M. J., **2**:131, 1957.
11. Coles, R. S., and Nathaniel, A.: The role of streptococcus in the pathogenesis of anterior uveitis. A.M.A. Arch. Ophth., **61**:45 (Jan.) 1959.
12. Hallett, J. W., Wolkowicz, M. I., Feria, Q. A., Leopold, I. H., and Wijewski, E.: Streptococcal serology in uveitis. A.M.A. Arch. Ophth., **61**:79 (Jan.) 1959.
13. Franceschetti, A.: Therapeutique Medicale Oculaire. Paris, Masson & Cie, 1957.
14. Sezer, N.: Further investigations on the virus of Behçet's disease. Am. J. Ophth., **41**:41 (Jan.) 1955.
15. France, R., Buchanan, R. N., Wilson, M. W., and Sheldon, M. B., Jr.: Relapsing iritis with recurrent ulcers of the mouth and genitalia (Behçet's syndrome). Medicine, **30**:335 (Dec.) 1951.
16. Uveitis: Survey Ophth., **4**: (June, Pt. II) 1959.

PRESENT STATUS OF THE ANTERIOR CHAMBER LENS*

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The possibility of replacing the cataractous lens with an intraocular artificial lens and thus obviating the need for aphakic spectacle lenses has intrigued ophthalmologists for generations. This was not successfully accomplished, however, until 1951 when Ridley of England reported the feasibility of such a procedure.[1-7] In his cases an extracapsular extraction was carried out with the posterior lens capsule left intact. An acrylic lenticulus was then placed behind the iris and supported in this location by the remaining posterior lens capsule and the iris diaphragm in the same position which the cataractous lens had previously occupied. It became immediately evident, and time has borne this out, that while success was frequently attained, there was a high incidence of complications. Dislocation of the lens into the vitreous and severe intractable plastic uveitis proved to be the most serious. In addition, when thickening of the posterior lens capsule occurred, discission was found to be most difficult. Because of this high incidence of complications the classical Ridley type operation has all but been abandoned. But be that as it may, Ridley must be credited with taking the first fateful step leading to successful substitution of plastic material for the natural lens.

On the other hand, it is almost impossible to determine what individual flash of genius was responsible for the concept of the anterior chamber lens. In any event, time was ripe for just such a procedure and, as so often happens in the scientific world, several individuals apparently conceived the idea independently at about the same time. Among those who should be given credit for this new concept are Strampelli,[8] Baron,[10] Bietti,[9] Schreck,[11] Scharf,[12] Dannheim[13] and Barraquer.[14] Strampelli,[8] however, was the first to publish an article on anterior chamber lenses and Baron[10] followed with an article only one month later.

As might be expected, each worker entertained a somewhat different opinion as to how the anterior chamber lens problem might best be solved, this being attested to by the multitude of different type anterior chamber lenses that have been introduced. One general principle, common to all, is that a small plastic lenticulus can be placed in the anterior chamber and held over the pupillary aperture by some type of supporting mechanism.

Since the introduction of anterior chamber lenses and more particularly since their refinement, the results obtained following their implantation have been infinitely superior to those obtained with the old Ridley technique and while there have been complications, these have been fewer in number and of much less severity. In the first place, the introduction of anterior chamber lenses is far less traumatic and if a lens with the proper size support is employed, there is practically no danger of dislocation. Instances of continued chronic uveitis have been rare and when present and necessitating removal of the lens, this is easily accomplished in contrast to the extraordinarily difficult task of removing a lens of the Ridley type. Furthermore, should discission become necessary, this is very easily carried out by simply slipping the discission knife behind the lens and carrying out the discission. A final advantage that the anterior chamber lens has over its antecedent is that it can be introduced in atraumatic fashion as a secondary procedure after the eye has become completely quiescent following the initial cataract extraction. This may in a large measure account for the rather signal suc-

* From the Department of Ophthalmology and Research Laboratory (Titmus), Medical College of Virginia. Read before the Chicago Ophthalmological Society, October 5, 1959.

cess that these lenses have attained.

Our department became interested in the anterior chamber lens problem in 1956 when we learned of the excellent results that Prof. Schreck had obtained with his lens. Prior to placing anterior chamber lenses in human cases, however, it was felt that a considerable amount of experimental work ought to be done and, accordingly, this was carried out in our laboratory. The following theoretical criteria regarding such a lens were set up:

Physical criteria

1. Aqueous humor dynamics should not be impaired by blockage of the angle with too large or too rigid a support.

2. Supports must be strong enough to maintain the lenticulus firmly in its proper place.

3. Both the lenticulus and its supports should be of such a size as to displace a minimum of aqueous.

4. The lens and its supporting mechanism should be as light as possible in order to prevent or minimize atrophy or hyperplasia of the supporting tissue.

5. The supports should be flexible, not only to reduce trauma at the time of introduction of the lens, but also to minimize the need for critical determination of the lens' supporting diameter and to reduce angle pressure of the support to a minimum.

6. The refractive index of the lens must be greater than that of the aqueous humor which is 1.36.

Chemical criteria

1. The material used for the lenticulus and for its support should be as chemically inert as possible to minimize the possibility of an explosive initial reaction or a long standing chronic inflammatory reaction.

2. The substance selected should in no wise disturb the electrolyte balance of the aqueous humor.

In order to evaluate these various factors, both physical and chemical, many animal experiments were carried out on rabbits, cats and dogs. Various sizes and shapes of acrylic strips were placed in the anterior chamber and careful observations were made over a period of many months. At varying intervals of time the eyes were enucleated and gross and histologic studies made. From these preliminary studies it was apparent that animal eyes tolerated implants of methyl methacrylate extraordinarily well. There was practically no initial reaction to the implantation of this material, nor was there any evidence of sustained irritation even after many months. It was also found that there was little or no reaction to nylon and Supramid which seemed to be the best materials available for flexible mounts.[15]

When it became evident that the various strips of methyl methacrylate were well tolerated a considerable number of Schreck lenses were implanted in the anterior chamber of dogs' eyes. While these lenses did not fit properly due to the difference in anterior chamber size of dog and man, a considerable amount of worthwhile knowledge was obtained in regard to the general tolerability of such lenses. Good results were obtained in 14 out of 16 operations.

Immediately after surgery on these dogs' eyes there was a moderate amount of congestion and some striate keratoplasty. In several cases a moderate amount of clouding remained for about a month in the region of the keratome section and in all instances where the anterior chamber lens remained in contact with the cornea irreversible opacification resulted. In none of these dogs' eyes was the normal lens removed and in no instance was cataract formation noted either as a result of implantation of the lens or of its continued presence thereafter. Immediately after the implantation of the lens and for some weeks following surgery fine brownish pigment spots could be seen on the surface of the lens and its support, but these disappeared completely in a matter of six weeks' time.

Histologic studies of these dogs' eyes at various intervals following implantation

were again negative for untoward reaction. We still have one dog alive with a Schreck type anterior chamber lens which was implanted well over three years ago. The appearance of this eye has not changed in that interval. The eye is still completely quiet and there has been no evidence of any untoward reaction, either inflammatory or dystrophic in type, except where the lens has remained in contact with the cornea. This area of the cornea is opaque, but this has remained static. Slitlamp examination of this eye does not reveal any subtle change over and above that noted grossly.

After satisfying ourselves that the anterior chamber lens was feasible and that complications could be expected to be minimal, it was felt that the time was propitious for placing lenses in the human eye. Only cases of unilateral aphakia were chosen since it was felt that such cases would benefit the most by obtaining binocularity and, in addition, risk would be reduced to a minimum since all patients would have one normal eye. We have not had the temerity to place anterior chamber lenses in myopes, anisometropes or following routine cataract extractions. From the first we have adhered strictly to this policy.

Two Schreck type lenses were first placed, according to the technique devised by Schreck, as follows: A small bevelled keratome incision was made just inside the limbus and enlarged with scissors. Two silk sutures were placed prior to introduction of the lenticulus. A spatula was then placed in the wound and passed across the anterior chamber to protect the pupillary area. The lenticulus was then introduced lengthwise by means of special curved forceps and after it had been placed completely in the anterior chamber, it was rotated sufficiently to remove the supports from the vicinity of the incision. The wound was then closed by means of the preplaced silk sutures. In both these cases there was a moderate amount of postoperative reaction which quieted down after several weeks of intensive steroid therapy. In one of these cases there was a short secondary rise of intraocular pressure, but this disappeared after 24 hours. Immediate visual results in these cases were good.

By this time we had developed a modification of the Dannheim lens[16] in which tangential flexible winglike mounts served as the supporting structure rather than the fixed inflexible mount employed by Schreck and others. Dannheim's original concept was to employ a biconvex lens in which loop supports were passed through the peripheral substance of the plastic lens. In contrast to this, in our lens the flexible mount was composed of a winglike loop of supramid threads which was affixed tangentially to the lens itself by means of peripheral grooves. By affixing the mounts tangentially a greater area of refracting lens surface is spared than is the case where the mounts are placed deep within the lens body. The advantages of both our lens and that of Dannheim are at once evident: (1) they are extraordinarily light; (2) the flexible mounts make for much simpler and atraumatic introduction; (3) the exact diameter of the anterior chamber does not have to be measured as the elasticity of the lens loops will allow for an error of 0.5 to 1.0 mm.; (4) the small size of the mount causes little or no blockage of the angle; (5) the methyl methacrylate material, as well as the supramid thread, is relatively inert; (6) the refractive index of the material used, methyl methacrylate, is 1.49 which is adequate for the necessary refracting power (aqueous humor = 1.36).

When our lens was used it was found that ease of insertion even with the Schreck technique was much greater and postoperative reaction was considerably less than with the Schreck lenses. As had been noted with both the Schreck lenses inserted in the dogs' eyes and the two Schreck lenses placed in human eyes, a large number of brownish pigment spots appeared on the anterior and posterior surface of the lenticulus. In one instance the patient stated that there was a slightly yellowish cast to her vision as a result of this.

In all instances these precipitates disappeared after one to two months' time and the visual results were satisfactory throughout.

After several experimental lenses had been successfully placed, we were able to obtain lenses which had been exquisitely polished and with markedly refined loops. A new technique of implanting the lenticulus which was much less time consuming and almost completely atraumatic was also developed. In this new technique a small spade-shaped keratome, slightly wider than the diameter of the lenticulus, was used to make the initial incision. This incision, bevelled in character, was made slightly inside the limbus. The lenticulus was then grasped by special forceps and forced sidewise through the wound, the resilient mount folding back as the lens passed into the anterior chamber. The lens was then passed well across the pupillary area until the flexible mounts had passed completely into the anterior chamber, at which time they expanded to assume their typical winglike shape, the tips of the mount thus coming to rest in the angle. It was not necessary to employ any sutures as the wound lips repositioned themselves properly as soon as the forceps were removed. It was found after a good many cases had been done that prior to implantation the pupil should be constricted to about 2.0 mm. in size. If it were larger than this, there was a tendency for the lenticulus to pass into the posterior chamber; while if it were smaller than this, postoperative dilatation became difficult.

Immediately after implantation of the lenticulus by means of the new or old technique, the pupil was widely dilated with atropine and 10-percent neosynephrine and intensive systemic steroid therapy was carried out. On the third day postoperatively intensive local steroid therapy was also begun, since a previous study revealed that such therapy in no wise slowed up the healing process or in any way weakened the wound.

Implantation of the new refined lenticulus by means of the new technique has resulted in minimal postoperative reaction in almost every case. Occasionally there has been an immediate slight to moderate striate reaction and in some instances a few fine brownish deposits on the lenticulus. These latter have been few in number and have disappeared completely in a matter of weeks. Occasional cells have usually been present for the first postoperative week and in a few instances there has been a trace of flare.

In one case where a "homemade" lens was employed, a moderately severe iridocyclitis persisted for a period of eight weeks and some post synechias formed. This reaction was thought to be due to acetone which had been used to cement the flexible mounts in place.

In another case, following insertion of a Dannheim type lens immediately following an intracapsular extraction (as a one stage procedure) a moderately severe iridocyclitis developed and persisted for six weeks. In this case a mild recurrent iridocyclitis, easily controlled with local steroids, has flared up several times since.

In one other instance, that of a congenital cataract which had been previously needled, there was a stormy postoperative course and it was feared that infection might be present and the lens might have to be removed. The eye quieted down, however, in a matter of five weeks and remained quiet until one month ago when it was found on follow-up that a mild iridocyclitis was present with synechias and a fairly thick secondary membrane. This reaction was so insidious that neither the patient, an 11-year-old Negro girl, nor her parents were aware of it. She appeared in answer to a letter asking for her to return for follow-up.

A summary of our cases to date follows: The two Schreck implants were both removed after about one year's time because of a moderately advanced dystrophy. There was slight improvement of the dystrophy following removal of the lenses.

None of our lenses or lenses of the

Dannheim type has had to be removed.* The first case of such an implant, a 14 year-old Negro boy with traumatic cataract followed by extracapsular extraction, has been in place now for 32 months. The eye has been completely quiet with a visual acuity of 20/20 uncorrected. This fell to 20/100 following the development of secondary membrane, but needling of this resulted in 20/20 vision with third-degree fusion.

There have been a total of 41 implants, two Schreck lenses and the remainder either Dannheim or Lieb-Guerry. All cases were unilateral aphakes of the following types (Dannheim and Lieb-Guerry only):

Traumatic	30
Congenital	3
Metabolic	3
Senile	2
Radiation	1

Visual acuities were as follows (six months follow-up):

		Age Group (yr.)	
24	20/20 to 20/30	4—1 to 10	5—50 to 60
6	20/30 to 20/50	14—10 to 20	2—60 to 70
3	20/50 to 20/80	1—20 to 30	1—above 70
1	No report on acuity	5—30 to 40	
5	To be needled	7—40 to 50	

Tropias were seen postoperatively in five cases, but 29 obtained binocular single vision. Five cases are yet to be needled and will require orthoptics and probably muscle surgery. Two of the tropias are improving following muscle surgery and orthoptics. In about one fourth of all cases an occasional very fine threadlike synechia has formed between the anterior iris surface and the posterior surface of the loop mounts. These have not prevented dilatation of the pupil and are apparently completely innocuous. Indeed, they can serve a very useful purpose since they prevent the rotation of a lens in which the mount is too short. Tonograms have been normal in all cases.

Complications have been minimal with our lens and/or the Dannheim lens, but as already mentioned both Schreck lenses had to be removed because of a progressive dystrophy. The following complications have been noted:

One case tilted lens (−3.0D. sph. ⊂ −3.0D. cyl., 20/50).

Two cases recurrent iridocyclitis, mild, controlled with local steroids: (a) Vision 20/30 when eye quiet, 20/70 when iridocyclitis active, radiation cataract, combined procedure—few synechias, eye now quiet; (b) Vision 20/100, stormy postoperative reaction (? infection), secondary membrane, numerous posterior synechias, few cells, and keratic precipitates on lens.

Two cases with eccentric location of lens over pupil; visual result, excellent.

In order to obtain comparative anterior chamber lens data, letters were sent to several continental workers interested in this field. Replies were received from the following: Barraquer, Bietti, Schreck and Wegner. Their experiences are now summarized.

Bietti[17] reports the following: "Over a period of five years 20 anterior chamber lenses were placed, 16 of them with good to excellent results." There was no long term follow-up data since Prof. Bietti moved from Parma to Rome and thus was unable to carry out such studies. There were two cases in which lenses had to be removed because of a "late Fuchs' dystrophy" and two lenses also had to be removed as a result of secondary glaucoma from synechias between iris and lens. He feels that "the main problem is how to avoid contact between lens and corneal endothelium and possibly also with the iris." He has decided to forego further implants until the problem has been further clarified. His last case was done over one year ago.

At the present time Prof. Joaquin Barraquer[18] has to his credit the most impressive series of anterior chamber lens implants.

* Since this paper was presented, the anterior chamber lens in the eye of the 11-year-old Negro girl was removed because of a chronic uveitis which failed to respond to therapy. The eye is now quiet but one-percent pilocarpine twice a day is necessary to control a mild glaucoma.

From 1954 until January 31, 1959, he has implanted a total of 411 lenses, these being of three different types; Strampelli 342, Dannheim 60, and Barraquer nine. He lists the following complications:

Strampelli type (342)

1. Corneal dystrophy due to contact with the endothelium, three cases.
2. Iridocyclitis with secondary glaucoma, three cases.
3. Macular edema (? relationship with anterior chamber lens), two cases.
4. Retinal detachment, two cases.

Dannheim type (60)

1. Transient iridocyclitis, three cases.
2. Corneal dystrophy, three cases (disappeared after sectioning one of mount loops).
3. Corneal dystrophy, two cases (irreversible).

Barraquer type (9)

1. Dystrophy from contact of support with endothelium with poorly constructed lens.

Barraquer also reports the necessity of substituting six Strampelli or Dannheim for a superior model and of sectioning the supramid loop in three cases to cure dystrophy. He further reports the complete removal (extraction) in 19 cases, or 4.6 percent. These statistics include experimental cases as well as trial lenses in useless eyes. Following removal of these lenses, in nine cases there was no improvement, while in 10 cases the complicating factor was completely reversible.

Barraquer sounds an optimistic note in this last report of his. He feels that while there have been complications, these are minimal and that the bête noire of such implants, corneal dystrophy, can be definitely prevented by properly designing a lens which, after introduction, will remain securely postioned without corneal touch. He feels that his lens more nearly approaches this ideal than any now extant.

Schreck[19,20] also reports an impressive number of cases. His statistics are as follows:

Total number of implants, 181 through March, 1959, and 156 through February, 1958, these 156 having been reported at the International Congress in Brussels. An analysis of the 156 cases follows:

119, unilateral aphakia after trauma
7, congenital cataracts (five unilateral, one bilateral)
18, unilateral heterochromia
7, unilateral cataracts of unknown etiology
5, anisometropia

The following complications were noted:
8, lenses rotated
12, cases of vitreous prolapse
7, mild infections
5, severe infections
12, lenses were removed, seven because of fibrous tissue proliferation and five because of keratopathy.

In Schreck's experience severe complications are caused by: (1) keratopathia postimplantation; (2) lesions of the anterior chamber angle; (3) chemical irritation due to sterilization of the lens; (4) mechanical irritation after the lens is implanted.

He made the following suggestions as a means of preventing complications: (1) no implantation of lenses in eyes with lesions of the chamber angle or posterior surface of the cornea; (2) anterior chamber lens should be neither too large nor too small and should have smooth edges; (3) sterilization of the lens with ultraviolet in order to eliminate chemical reaction; (4) substitution of silicone for methyl methacrilate.

In another personal communication Prof. Wilhelm Wegner[21] of Freiburg reports his experiences as follows:

Total number of cases 31—all Dannheim lenses:
24—traumatic aphakia
3—myotomic cataract
3—senile cataract
1—heterochromic

Observation period three to 38 months. Postoperative iritis seen occasionally and controlled with antihistamine and cortisone.

22 cases show fine synechias fixing mounts.

Lenses removed, one cause: intractable secondary glaucoma in heterochromia.

Vision: 25—20/30 or better
3—20/40
2—20/100 to 20/200

Stereopsis	24
Normal retinal correspondence	25
Suppression	4
Diplopia	1

Advantages of the Dannheim type lens:

1. Implantation technique simple.
2. Little postoperative implant reaction.
3. Patient has "sensation of normal vision."

Contraindications:

1. Glaucoma.
2. Intraocular inflammation.
3. Diabetes.
4. Hemorrhagic tendency.
5. Myopia.

In the hope of finding a material more suitable for anterior chamber lenses, a study was completed about one year ago in our laboratory.[15] In this study nine different plastic materials were implanted in rabbit eyes for the purpose of determining their tolerability. These various plastic resins were selected on the basis of their optical qualities. The materials were:

1. CR-39 Homalite Corporation
2. CR-39 Pittsburgh Plate Glass
3. Gafite, General Anilin and Film Corporation
4. Lexan, General Electric Corporation
5. Lucite, DuPont Company
6. Plexiglas, Rohm and Hass Company
7. Silicone, Dow Corning Company
8. Styrex 767, Dow Chemical Corporation
9. Styron 666, Dow Chemical Corporation

During the 10 months' observation period with histologic examinations of enucleated eyes, Silicone B 695-106-1 and Lucite proved to be the least irritating materials. Silicone was definitely the most inert as shown by the growth of a one cell thick layer of endothelial cells on the surface of the implanted material. Its refractive index of 1.49 and light transmission of 90 percent, without discoloration, make it even more ideal.

Lucite, chemically a methyl methacrylate, has approximately the same optical qualities as Silicone. Due to its higher surface activity, however, with slow elimination of chemical disinfectants, a prolonged mild irritation of the eye may occur. This can be minimized by sterilizing the material with ultraviolet radiation. In our experiments, while reaction was minimal, it was still definitely more pronounced than that obtained with Silicone. This coincides with Schreck's findings.

Of the plastic materials considered where optical qualities were not of importance, Supramid and Teflon gave the least tissue reaction. Supramid, produced by polycondensation of E-Caprolactam, is very well tolerated by body tissue. Although occasionally a mild foreign body reaction may be produced, this is always of short duration and is possibly due to chemical disinfectants. It remains one of the most inert materials among the large number of plastic resins usable for implantation purposes in the human.

Teflon, a tetrafluorethylene resin, is almost identical to Supramid in regard to its tissue tolerability.

Discussion

In our experience, complications resulting from placement of anterior chamber lenses of either the Dannheim or Lieb-Guerry type have been minimal. In our series there has been to date no single instance of dystrophy with these type lenses, although both our cases where a Schreck lens was implanted resulted in dystrophy. In these two cases there was a slight posterior corneal touch by the fixed mounts which was undoubtedly responsible. In each instance the dystrophy was not at once apparent, but appeared about nine months following implantation. Since the longest duration of our lens in this series has been only 32 months, there is still the possibility that dystrophies will occur. This has been reported by both Schreck and Barraquer after two to three years. To feel safe, therefore, our cases must pass the test of time, that is, the passage of at least another year or so. After that, it is extremely doubtful that dystrophy will occur.

While dystrophies after three years are very rare, they apparently can occur. This is emphasized in a paper by Wollensak[22] of Schreck's clinic given at the resent Heidelberg Congress. He reports that dystrophies

have occurred many years after implantation; not only in the case of anterior chamber lenses, but also where posterior chamber lenses of the Ridley type have been employed. He feels that while dystrophy may be caused or at least augmented by a poorly fitting lens with corneal touch, this is far from the whole story and certainly is not the modus operandi where dystrophic changes occur with a Ridley type lens.

In his search for other factors, Wollensak incriminates: (1) disinfectants used in sterilizing the anterior chamber lens, and (2) degradation products of the acrylic material itself. In favor of this first factor causing mischief, he cites the following:

Dehydrase activity of corneal tissue is decreased in zephiran 1:8,000, and various disinfectants are toxic to tissue cultures of fibroblasts. Ultraviolet sterilization does not solve the problem completely either, since irradiation gives rise to such breakdown products as CO_2 and aldehydes which are toxic.

In regard to the second factor, he feels that the peroxides employed as catalysts in the manufacture of acrylic material are not completely eliminated and may act abiotically. He cites further evidence of acrylic degradation by demonstrating erosion on the surface of the lenses removed from dystrophic cases. Apparently these erosions have resulted from acrylic material going into solution, and it is his feeling that such material may be toxic although he has been unable to identify these products chemically.

From this study, he concludes: (1) severe cases of dystrophy occur at an average age of 43 years; (2) mild cases occur at an average age of 26 years; (3) keratopathy can occur after many years, both in anterior chamber and posterior chamber acrylic lenses. The cause is an endothelial dystrophy.

In my opinion, the final word on postimplantation dystrophy is yet to be said. If such is found to occur late and is the result of toxic breakdown products, a more inert material will have to be substituted. Further studies along such lines are indicated. Until such dystrophies are seen in our cases where postcorneal touch is not present, I lean toward the mechanical theory of causation. Should a dystrophy begin, from Barraquer's experience, it should be readily reversible following early extraction of the offending lens.

Careful selection of cases for anterior chamber lens implantation is, perhaps, the greatest single factor in determining a successful outcome. As already mentioned, we have placed lenses only in cases of unilateral aphakia and, in addition, have adhered to a rather rigid code of contraindications. These may be summarized as follows:

Physical contraindications

1. Secondary or primary glaucoma.
2. Vitreous in the anterior chamber.
3. Dense secondary cataracts unless properly discissed.
4. Eyes which are predisposed to sympathetic ophthalmia.
5. Nongranulomatous or granulomatous uveitis.
6. Any fundus pathology, especially macular degeneration and old reattached retinal separations.
7. All cases which show gonioscopically a narrow angle.
8. Corneal degenerations.
9. Shallow anterior chamber.
10. Fixed pupil, due to posterior vitreous synechias.

Philosophical contraindications

Other methods should be used when there are other simpler and more conventional solutions for such problems as:

1. Myopia.
2. Anisometropia.
3. Routine cataract extraction.

Along this same line, it is my feeling that anterior chamber lens implantation should

be a two-stage procedure. In only two cases have lenses been implanted at the time of cataract extraction and in both instances postoperative reaction was rather marked. On the other hand, when the lens is implanted some time following cataract extraction, and where our new implantation technique is employed, postoperative reaction is minimal. Indeed, in most instances the eye shows almost no reaction and the little that is apparent subsides quickly.

Summary and Conclusion

At the present time, in selected cases, the anterior chamber lens with flexible mounts offers the best solution for the problem of monocular aphakia.

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References

1. Ridley, H.: Intraocular acrylic lenses. Tr. Ophth. Soc. U. Kingdom, **71**:617, 1951.
2. ———: Artificial intraocular lenses after cataract extraction. St. Thomas's Hosp. Rep., Series 2, **7**:12, 1951.
3. ———: Intraocular acrylic lenses: A recent development in the surgery of cataract. Brit. J. Ophth., **36**:113, 1952.
4. ———: Intraocular acrylic lenses after cataract extraction. Lancet, **1**:118, 1952.
5. ———: Further observations on intraocular acrylic lenses. Tr. Ophth. Soc. U. Kingdom, **72**:511, 1952.
6. ———: Further observations on intraocular acrylic lenses in cataract surgery. J. Internat. Coll. Surgeons, **18**:825, 1952.
7. ———: Further observations on intraocular acrylic lenses. Tr. Am. Acad. Ophth., **57**:98, 1953.
8. Strampelli, B.: Sopportabilita di lenti acriliche in camera anteriore nella afachia e nei vizi di refrazione. Ann. oftal. & clin. Ocul., **80**:75, 1954.
9. Bietti, G. B.: The present state of the use of plastics in eye surgery. Acta. Ophth., **33**:337, 1955.
10. Baron, A.: Bull. Soc. Ophtal. France, Nov. 1953, No. 8.
11. Schreck, E.: Vorderkammerlinsen zur Behandlung der Aphakie und hoher Ametropien. 59 Ber. Deutsch. Ophth. Gesell., Heidelberg, 1955, p. 212.
12. Scharf, J.: Ueber zweijahrige Erfahrungen mit einer Vorderkammerlinse. 59 Ber. Deutsch. Ophth. Gesell., Heidelberg, 1955, p. 222.
13. Dannheim, H.: Vorderkammerlinse mit elastischen Halteschlingen. 59 Ber. Deutsch. Ophth. Gesell., Heidelberg, 1956, p. 222.
14. Barraquer Moner, J.: Lentes plasticos de camara anterior. Estud inform Oftal. (Barcelona), 1954, chap. 15, p. 6.
15. Lieb, W. A., Geeraets, W. J., Guerry, D., III, and Dickerson, J.: Tissue tolerance of plastic resins: Experimental study of their physical, chemical and histopathologic reactions (Part I). EENT Month., **38**:210-215 (Mar.) 1959; Part II. EENT Month., **38**:303-321 (Apr.) 1959.
16. Lieb, W. A., and Guerry, D., III: Anterior chamber Lenses for refractive correction of unilateral aphakia. Am. J. Ophth., **44**:579 (Nov.) 1957.
17. Bietti, G. B.: Personal communication.
18. Barraquer Moner, Jr.: Personal communication.
19. Schreck, E.: Tr. XVIII Internat. Congr. Ophth., 1958.
20. ———: Personal communication.
21. Wegner, W.: Personal communication. Reported at Deutsche Ophthalmologische Gesellschaft, Heidelberg, 1959.
22. Wollensak, J.: Personal communication. Reported at Deutsche Ophthalmologische Gesellschaft, Heidelberg, 1959.

CHANGES OF CENTRAL RETINAL ARTERY PRESSURE*

Induced by common carotid artery compression

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The diagnostic value of retinal artery pressure changes which occur as a result of impaired carotid circulation has been established by several authors.[1–5]

Retinal artery pressure determination is a simple and harmless procedure. An attempt was made to establish normal values in healthy subjects of different ages. Ophthalmodynamometry was performed before and during compression of the common carotid artery.

The present report deals only with normal data. These will be of value in comparison with figures obtained from pathologic cases.

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Material and Method

Subjects with neither visual nor neurologic diseases were chosen. They were divided into four groups of 10 individuals each: Group I, 31 to 40 years of age; Group II,

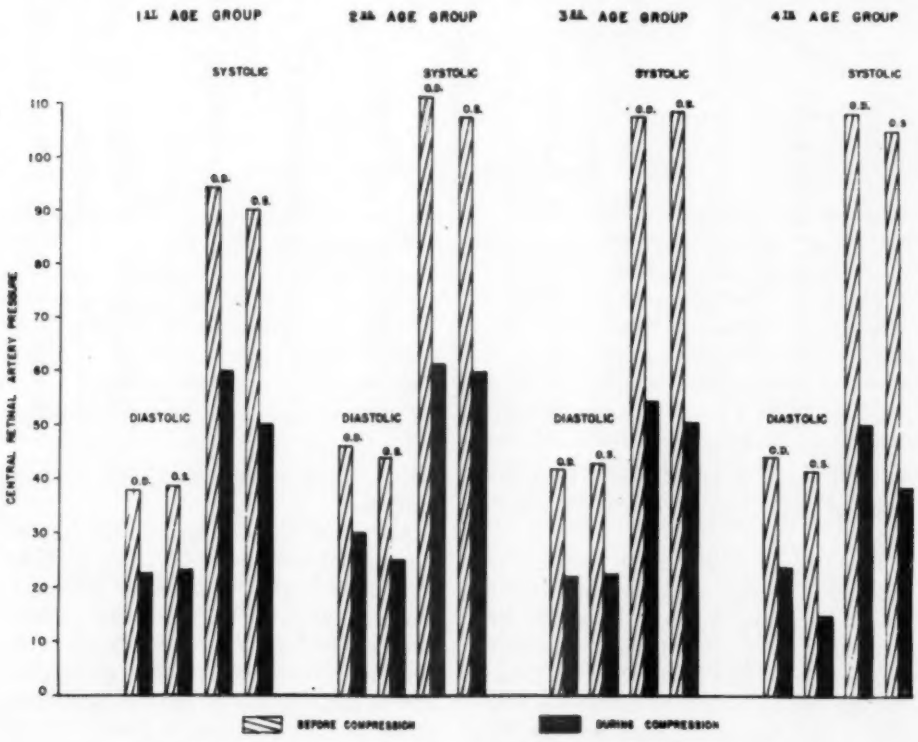

Chart 1 (Carvalho, et al.). Common carotid artery compression.

TABLE 1

MEASUREMENTS FOR DIASTOLIC AND SYSTOLIC PRESSURES

Case	Age (yr.)	Sex	Right Eye				Left Eye			
			Diastolic before Compression	Pressure during Compression	Systolic before Compression	Pressure during Compression	Diastolic before Compression	Pressure during Compression	Systolic before Compression	Pressure during Compression
1	31	F	32	20	87	52	42	10	79	49
2	31	F	45	36	87	63	42	33	84	42
3	31	M	25	5	92	52	30	25	91	65
4	32	M	45	25	100	45	45	26	90	37
5	32	F	52	35	102	55	39	35	95	60
6	32	F	35	20	87	55	35	26	85	80
7	33	M	35	25	102	55	36	20	89	57
8	37	F	45	31	105	85	47	32	97	62
9	34	F	30	5	70	40	25	5	75	20
10	40	F	34	25	107	45	43	20	110	42
11	43	F	25	20	70	50	25	10	80	50
12	43	F	30	17	130	52	30	30	132	65
13	44	F	55	35	123	62	55	25	110	60
14	44	F	35	15	97	42	30	17	90	33
15	44	F	42	30	107	65	40	25	82	62
16	46	M	60	40	115	70	60	30	115	70
17	47	F	57	45	120	90	60	30	115	70
18	48	F	45	26	110	65	42	28	117	60
19	50	M	60	40	125	70	65	31	130	75
20	50	F	47	30	110	50	40	27	110	35
21	51	F	22	20	92	52	21	5	93	36
22	52	M	57	22	115	52	40	25	125	42
23	54	F	65	35	140	85	47	30	115	69
24	54	F	45	30	122	65	52	40	120	60
25	55	F	27	15	65	41	27	10	65	29
26	56	M	40	30	107	67	50	10	110	62
27	56	F	37	25	130	65	50	31	150	95
28	57	M	35	5	88	32	35	20	95	32
29	57	M	50	10	120	25	50	35	117	52
30	58	M	47	26	95	59	59	26	100	35
31	61	M	60	35	125	62	57	30	127	67
32	61	M	40	27	100	50	60	30	120	55
33	61	M	42	10	97	25	25	10	70	25
34	61	M	37	22	97	47	40	10	100	37
35	62	M	52	17	122	57	45	20	122	37
36	62	M	45	25	110	47	45	5	95	32
37	62	M	32	15	120	51	30	5	107	30
38	63	M	50	27	107	50	37	20	110	35
39	67	F	37	22	87	45	35	17	95	42
40	69	F	49	35	122	75	45	5	115	25

41 to 50 years of age; Group III, 51 to 60 years of age; Group IV, 61 to 70 years of age.

First, the humeral blood pressure was measured. The intraocular pressure was recorded after mydriasis with 10-percent Neosynephrine drops. Ophthalmodynamometry was performed first on the right and then on the left eye according to the classical technique. The instrument used was the Bailliart ophthalmodynamometer with a dial. Two measurements for both diastolic and systolic pressure were made and the mean computed.

After this, digital compression of the common carotid was performed, using the index and middle fingers of one hand. The vessel was pressed against the spine until pulsation could not be felt by the index finger of the other hand. When the intended stage of occlusion of one side was reached, measurements of the diastolic and systolic pressure in the ipsilateral retinal artery were taken. Two determinations both for diastolic and sys-

TABLE 2

ANALYSIS OF VARIATIONS

Source of Variation	Degrees of Freedom	Sum of the Squares	Mean Square	F*
Between individuals†	36	31,692.563	88.035	
Between eyes (right and left)	1	533.024	533.024	533.024/ 50.943= 10.463
Between pressures (diastolic and systolic)	1	165,938.653	101,938.653	165,938.653/175.467=945.697
Between times (before and during compression)	1	101,068.653	101,068.653	101,068.653/119.552=845.395
Between ages	3	3,743.434	1,247.811	1,247.811/ 88.035= 14.174
Interaction individual×eye†	36	1,833.969	50.943	
Interaction individual × pressure†	36	6,316.812	175.467	
Interaction individual×time†	36	4,303.862	119.552	
Interaction eye×pressure†	1	71.257	71.257	71.257/ 31.179= 2.285
Interaction eye×time	1	136.503	136.503	136.503/147.013= 0.928
Interaction eye×age	3	386.135	128.712	128.712/ 50.943= 2.527
Interaction pressure×time	1	21,336.776	21,336.776	21,336.776/ 82.014=260.160‡
Interaction pressure×age	3	556.910	185.637	185.637/175.467= 1.058
Interaction time×age	3	3,041.860	1,013.953	1,013.953/119.552= 8.481
Individual×eye×pressure†	36	1,122.463	31,179	
Individual×eye×time†	36	5,292.456	147.013	
Individual×pressure×time†	36	2,952.513	82.014	
Eye×pressure×time	1	3.831	3.831	3.831/ 37.841= 0.101
Eye×pressure×age	3	46.659	15.553	15.553/ 31.179= 0.499
Eye×time×age	3	134.659	44.886	44.886/147.013= 0.305
Pressure×time×age	3	722.086	240.695	240.695/ 82.014= 0.293
Individual×eye×pressure ×time	36	1,362.262	37.841	
Eye×pressure×time×age†	3	48.282	16.094	16.094/ 37.841= 0.425
	319	352,645.622	1,105.472	

* F—See distribution table.
† Within age groups.
‡ Significant value at the one-percent level for one and 36 degrees of freedom.

tolic pressure were made and the mean computed. The right eye was always examined first. The tonometer and the ophthalmodynamometer used were always the same. The whole examination was carried out with the patient in a supine position. All the retinal artery pressure determinations and neck compressions were made by the same observers (C. A. C. and J. A. F. C.).

The intraocular pressure was within normal range in all patients. Figures presented in this paper are direct readings from the ophthalmodynamometer dial.

Prolonged pressure on the eye was avoided so that aqueous dynamics were not influenced. No patient showed symptoms of cerebral ischemia during carotid compression.

RESULTS AND COMMENTS

The measurements for diastolic and systolic pressures for both eyes, before and during common carotid compression in the four age groups are shown in Table 1 and chart 1. The variances analyses to which the measurements were submitted are shown in Table 2. The effect of common carotid compression on retinal artery pressures is different for the diastolic and systolic pressures according to the F values ($F = 260, 160$; see Table 2). On the other hand, the changes in diastolic and systolic pressure induced by common carotid compression are similar in the four age groups and in both eyes. They behave in a similar fashion ($F = 0.425$; see Table 2). For this reason the values for the right and left eyes in each case were combined and the mean computed. The effect of common carotid compression on the retinal artery pressure was then statistically evaluated, taking into consideration only average values for the diastolic and systolic pressures.

TABLE 3

DIASTOLIC PRESSURE FOR BOTH EYES

Age (yr.)	Before Compression	During Compression	Δ' = Before -During
31–40	74	30	44
	87	69	18
	55	30	25
	90	51	39
	91	70	21
	70	46	24
	71	45	26
	92	63	29
	55	10	45
	77	45	32
TOTAL	762	459	303
MEAN	76.2	45.9	$\Delta_1' = 30.3$
41–50	50	30	20
	60	47	13
	110	60	50
	65	32	33
	82	55	27
	120	70	50
	117	75	42
	87	54	33
	125	71	54
	87	57	30
TOTAL	903	551	352
MEAN	90.3	55.1	$\Delta_2' = 35.2$
51–60	43	25	18
	97	47	50
	112	65	47
	97	70	27
	54	25	29
	90	40	50
	87	56	31
	70	25	45
	100	45	55
	106	52	54
TOTAL	856	450	406
MEAN	85.6	45.0	$\Delta_3' = 40.6$
61–70	117	65	52
	100	57	43
	67	20	47
	77	32	45
	97	37	60
	90	30	60
	62	20	42
	87	47	40
	72	39	33
	94	40	54
TOTAL	863	387	476
MEAN	86.3	38.7	$\Delta_4' = 47.6$
GENERAL TOTAL	3384	1847	1537
GENERAL MEAN	84.6	46.2	$\bar{\Delta}' = 47.6$

$s_{\Delta'} = 11.48$; $s_{\bar{\Delta}'} = 11.48/\sqrt{40} = 1.82$.
$t = 38.4/1.82 = 21.09$ which is significant at the 1% level for 36 degrees of freedom.

TABLE 4

SYSTOLIC PRESSURE FOR BOTH EYES

Age (yr.)	Before Compression	During Compression	Δ = Before-During
31–40	166	101	65
	171	105	66
	183	117	66
	190	82	108
	197	115	82
	172	135	37
	191	112	79
	202	147	55
	145	60	85
	217	87	130
TOTAL	1834	1061	773
MEAN	183.4	106.1	$\Delta_1 = 77.3$
41–50	150	100	50
	262	117	145
	233	122	111
	187	75	112
	189	127	62
	230	140	90
	235	160	75
	227	125	102
	255	145	110
	220	85	135
TOTAL	2188	1196	992
MEAN	218.8	119.6	$\Delta_2 = 99.2$
51–60	185	88	97
	240	94	146
	255	154	101
	242	125	117
	130	70	60
	217	129	88
	280	160	120
	183	64	119
	237	77	160
	195	94	101
TOTAL	2164	1055	1109
MEAN	216.4	105.5	$\Delta_3 = 110.9$
61–70	252	129	123
	220	105	115
	167	50	117
	197	62	135
	244	94	150
	205	79	126
	227	81	146
	217	85	132
	182	87	95
	237	100	137
TOTAL	2148	872	1276
MEAN	214.8	87.2	$\Delta_4 = 127.6$
GENERAL TOTAL	8334	4184	4150
GENERAL MEAN	208.35	104.60	$\bar{\Delta} = 103.75$

$s_{\Delta} = 25.98$*; $s_{\bar{\Delta}} = 25.98/\sqrt{40} = 4.11$.
$t = 103.75/4.11 = 25.243$ which is significant at the 1% level for 36 degrees of freedom.

Both the diastolic and systolic pressures of the retinal artery during common carotid artery compression show a significant decrease at the level of one percent of their values. This can be see in Tables 3 and 4, where "t" is, respectively, equal to 21.09 and 25.243. On the other hand, the fall of the systolic pressure during compression is significantly greater than that of the diastolic pressure ("t" is equal to 16.13; see Table 5).

Because of its clinical value, the confidence interval of the difference between right and left eyes was determined for diastolic and systolic pressures before and during common carotid compression in the four age groups (table 6). Similarly, the confidence interval of the diastolic (before minus during) and systolic (before minus during) pressures in the same eye were determined (table 7).

Any interference in the blood flow in the carotid system can be suspected if measurements larger than those presented in Table 6 or 7 are found in a given case.

Summary

Central retinal artery pressures were determined before and during common carotid artery compression in 40 healthy subjects. The measurements obtained were statistically evaluated. The confidence interval was determined (1) of the differences between right and left eyes and (2) of the diastolic (before compression minus during compression) and systolic (before compression minus during compression) pressures in the same eye.

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TABLE 5

VALUES OF THE DIFFERENCE

Age Group	$\delta = \Delta - \Delta'$
I.	21
	48
	41
	69
(31–40)	61
	13
	53
	26
	40
	98
TOTAL	Σ 470
MEAN	$\delta_1 = 47.0$
II.	30
	132
	61
	79
(41–50)	35
	40
	33
	69
	56
	105
TOTAL	Σ 640
MEAN	$\delta_2 = 64.0$
III.	79
	96
	54
	90
(51–60)	31
	38
	89
	74
	105
	47
TOTAL	Σ 703
MEAN	$\delta_3 = 70.3$
IV.	71
	72
	70
	90
(61–70)	90
	66
	104
	93
	62
	83
TOTAL	Σ 800
MEAN	$\delta_4 = 80.0$
GENERAL TOTAL	1623
GENERAL MEAN	$\delta = 65.32$

Systolic (before-during)
Diastolic (before-during)
For both eyes.
$s_\delta = 25.61/\sqrt{40} = 4.05$
$t = 65.32/4.05 = 16.13$ which is significant at the 1% level for 36 degrees of freedom.

* *Footnote to Table 4*

$$s_\Delta = \sqrt{\frac{\sum_{i=1}^{4}\sum_{j=1}^{10}(\Delta ij - \bar{\Delta} i)^2}{36}} = \sqrt{\frac{24.307}{36}} = 25.98$$

See table of the "t" distribution.

TABLE 6

NINETY-FIVE PERCENT CONFIDENCE-INTERVAL ESTIMATE OF THE MEAN OF THE DIFFERENCE

(right eye minus left eye)

Age Group	Diastolic		Systolic	
	Before Compression	During Compression	Before Compression	During Compression
I 31–40	$-0.6\pm2.021^{*}\times2.625^{\dagger}$ $=-0.6\pm5.305$ -5.9–4.7	$-0.5\pm2.021\times3.262^{\ddagger}$ $=-0.5\pm6.592$ -7.1–6.1	$4.4\pm2.021^{*}\times3.191^{\S}$ $=4.4\pm6.449$ -2.0–10.8	$3.3\pm2.021\times4.944^{\#}$ $=3.3\pm9.992$ -6.7–13.3
II 41–50	0.9 ± 5.305 -4.4–6.2	4.5 ± 6.592 -2.1–11.1	2.6 ± 6.449 -3.8–9.0	3.6 ± 9.992 -6.4–10.0
III 51–60	-0.6 ± 5.305 -5.9–4.7	-1.4 ± 6.592 -8.0–5.2	-1.6 ± 6.449 -8.0–4.8	3.1 ± 9.992 -6.9–13.1
IV 61–70	2.5 ± 5.305 -2.8–7.8	8.3 ± 6.592 -1.7–14.9	2.6 ± 6.449 -3.8–9.0	12.4 ± 9.992 2.4–22.4

* Is the standard error estimate for the mean of the difference.

† $2.625=\frac{8.30}{\sqrt{10}}$ ‡ $3.262=\frac{10.315}{\sqrt{10}}$ § $3.191=\frac{10.090}{\sqrt{10}}$ # $4.944=\frac{15.633}{\sqrt{10}}$

TABLE 7

NINETY-FIVE PERCENT CONFIDENCE-INTERVAL ESTIMATE OF THE MEAN OF THE DIFFERENCE

(before compression minus during compression)

Age (yr.)	Diastolic	Systolic
31–40	$30.3\pm2.021^{*}\times3.629^{\dagger}=30.3\pm7.30$ 23.0–37.6	$77.3-2.021^{*}\times8.217^{\ddagger}=77.3-16.6$ 60.7–93.9
41–50	35.2 ± 7.3 27.9–42.5	99.2 ± 16.6 82.6–115.8
51–60	40.6 ± 7.30 33.3–47.9	111.9 ± 16.6 95.3–128.5
61–70	47.6 ± 7.30 40.3–54.9	127.6 ± 16.6 111.0–144.2
TOTAL	$38.4-2.021\times1.82=38.4-3.70$ 34.7–42.1	$103.75-2.021\times4.11=103.75-8.31$ 95.4–112.1

* 2.021 is the 0.975 percentile of the "t" distribution for 36 degrees of freedom.

† $3.629=11.48/\sqrt{10}$ is the standard error estimate for the mean of differences.

‡ $8.217=25.98/10$ is the standard error estimate for the mean of differences.

REFERENCES

1. Van Allen, M. W., and Blodi, F. C.: Retinal artery blood pressure changes with compression or ligation of the carotid arteries. Am. J. Ophth., **45**:364-371, 1958.

2. Heyman, A., Karp, H. R., and Bloor, B. M.: Determination of retinal artery pressures in diagnosis of carotid artery occlusion. Neurology, **7**:97-104, 1957.

3. Milleti, M.: Le diagnostic de la thrombose primitive de la carotide interne: Pressé Med., **54**:655-656, 1946.

4. Svien, H. J., and Hollenhorst, R. W.: Pressure in retinal arteries after ligation or occlusion of the carotid artery. Proc. Staff Meet. Mayo Clinic, **31**:684-692, 1956.

5. Hollenhorst, R. W.: Thrombosis of internal carotid artery. Am. J. Ophth., **47**:753-767, 1959.

CONJUNCTIVAL TUBERCULOSIS*

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External ocular tuberculosis of the conjunctiva is, at present, an extremely rare disease. Isolated cases have been reported in recent years [2, 4, 7–9, 11, 13–16, 21, 22] but statistical data regarding the incidence of this disease is difficult to obtain. Eyre[6] (1912) reported an incidence of 1:2,500 among patients with ocular complaints, compiled in an area where frequency of tuberculosis was relatively high.

HISTORY[6]

The first case of conjunctival tuberculosis was reported by Koester (1873) followed by Sattler's report (1874). The diagnosis was based on clinical evidence and the finding of granulomas in the lesions histologically. Koch (1882) demonstrated bacilli in the tuberculous lesions. The publication of this data provoked a series of reports of conjunctival tuberculosis which were based on sound scientific criteria. Sattler (1891) formulated a clinical classification of the conjunctival lesions based on the morphology of the lesion.

INCIDENCE

The exact incidence of conjunctival tuberculosis is unknown. In recent years with the marked decline in the incidence of systemic tuberculosis, the occurrence of conjunctival tuberculosis has concomitantly decreased. Bruce and Locatcher-Khorazo[1] reported that Bordley had found no case among 41,730 patients treated at the Baltimore Eye, Ear, Nose and Throat Charity Hospital. They also stated that conjunctival tuberculosis had not been recorded at the Institute of Ophthalmology at Presbyterian Medical Center up to 1947.

The majority of cases are found in individuals under 20 years of age. Females are affected twice as commonly as males.[6, 17]

ROUTE OF INFECTION

The predominant paths of infection are:

1. Direct extension—this occurs from surrounding tuberculous lesions such as lupus.

2. Direct inoculation—Eyre[6] suggested that this is the method of infection in the majority of cases. The source may be:

a. Contact with actively infected individuals

b. Contaminated articles of clothing

c. Dried particles of infected material in the air

d. Fingers which have come in contact with infected milk

3. Endogenous source (metastatic)—this occurs via the blood stream in an individual who has an active or apparently inactive[22] focus in some other part of the body. Eyre was unable to produce this experimentally in rabbits. He therefore concluded that this type of infection was extremely rare.

CLINICAL PICTURE

The clinical picture is characterized by a protean symptomatology and pleomorphic appearance. The complaints may be trivial (as they are in the majority of cases), or severe. There may be complaints of redness of the affected eye, discomfort, mucopurulent discharge, lacrimation, swelling and edema of the lids. A regional lymphadenitis is present in the majority of cases. Rarely, this finding may be absent.[9] Caseation of the involved nodes is often present. The condition is predominantly unilateral. Bilat-

* From the Research Department of the New York Eye and Ear Infirmary. Dr. Brittain F. Payne kindly granted permission to report this case from his service.

erality is more characteristic of secondary rather than primary infection. The palpebral conjunctiva is more frequently involved than the bulbar conjunctiva.

Clinical classification

Clinically the disease may be considered under three basic headings:

I. Type (a) primary—exogenous infection in an individual not previously infected; (b) secondary—exogenous, or endogenous, either metastatic or from a contiguous focus of infection.

II. Morphologic appearance. The clinical classification which is generally accepted is essentially that proposed by Sattler.

1. *Ulcerative.* This usually occurs on the tarsal conjunctiva with early ulceration. It begins as small miliary ulcers with sharp edges, serrated and slightly raised, with an uneven base and filled with grayish yellow slough. Later these small ulcers tend to coalesce.

2. *Miliary tubercles.* These also occur predominantly on the tarsal conjunctiva in the form of grayish or yellowish nodules which affect only a small area. There is usually a regional lymphadenitis. In the later stages the cornea may show pannus with small grayish red nodules.

3. *Hypertrophic granulations.* This type is characterized by massive red hypertrophied papillae with flattened mushroom-shaped masses of granulation tissue on the tarsal conjunctiva. Necrosis may occur to form ulcers. The intervening conjunctival tissue may appear normal except for a livid purple red hue.

4. *Lupus.* This is an extension of true lupus from adjacent areas of skin and mucous membrane. It presents as jellylike masses either pale and grayish, or deep crimson in color. Ulceration may occur.

5. *Pedunculated tumor.* This type is characterized by a pedunculated polypoid tumor arising from the tarsal or bulbar conjunctiva. The regional nodes are not involved. There is no discharge.

6. *Conjunctival tuberculoma.* This subdivision was added to the present classification by Duke-Elder[3] in place of Subdivision 4, entitled lupus. This type of lesion was described by Jordan (1932). The lesion is characterized by a hard, solid, yellow or red tumor which occurs in the subconjunctival tissues and is covered by epithelium. There is no tendency to ulceration and there is no discharge from the eye. The remainder of the conjunctiva remains essentially normal.

III. Anatomic location. Tuberculosis may involve any part of the conjunctiva. The incidence according to anatomic location reported by Villard is: palpebral 70 percent, bulbar 22 percent, fornix eight percent.[12]

Diagnosis

Positive diagnosis of conjunctival tuberculosis can only be positively made by histologic study of a biopsy specimen or by isolation of the tubercle bacillus itself. Only 25 percent of the cases reported in the literature up until 1950 showed the tubercle bacillus on examination of secretions or excised tissue.[9] The following factors must be taken into consideration in confirming the diagnosis:

1. The history of the disease
2. The clinical appearance of the lesion
3. Culture and isolation of the tubercle bacillus from the lesion
4. Guinea-pig inoculation
5. Subsequent recovery of the organism
6. Histologic study of a biopsy specimen
7. Elimination of other disease (see under differential diagnosis) by clinical and laboratory study
8. The response of the patient to antituberculous medication
9. Mantoux skin reaction. This may be helpful if the lesion has been present for more than seven weeks and if no other focus of infection can be found in the individual.

Differential diagnosis

Since conjunctival tuberculosis presents

such a varied clinical appearance, many diseases must be considered in the differential diagnosis:

1. Parinaud's ocular glandular syndrome —when caused by tularemia and leptothrix infections.[20]
2. Trachoma
3. Syphilis
4. Simple follicular conjunctivitis
5. Vernal catarrh
6. Phlyctenular conjunctivitis
7. Episcleritis
8. Epithelioma and rodent ulcer
9. Beginning lipomas and adenomas
10. Parasitic and dermoid cysts
11. Simple granulation tumor
12. Pustules of anthrax and vaccinia
13. Angioma

Treatment

Prior to the advent of antibiotics, the treatment of this disease presented a formidable problem. Radical excision of the lesion, local ultraviolet light, X-ray therapy, Iodoform powder, bland irrigations, and oral potassium iodide solution were attempted.[19]

Fig. 1 (Anhalt, Zavell, Chang and Byron). A picture showing the circumscribed, elevated, pinkish-yellowish mass near the limbus of the right eye. The cornea shows some limbal infiltration. There is marked congestion of the bulbar and conjunctival vessels. This photograph was taken on June 27, 1958.

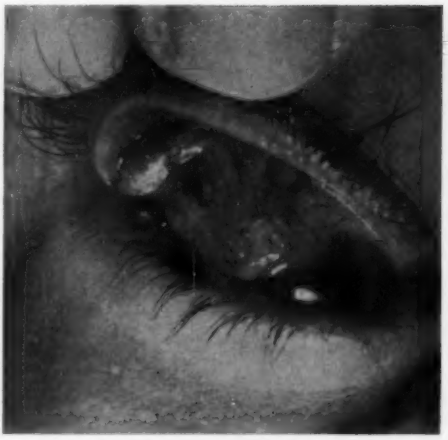

Fig. 2 (Anhalt, Zavell, Chang and Byron). A photograph to show the decrease in the size of the ocular lesion on therapy with Isoniazid and PAS. This photograph was taken September 2, 1958, after five days of therapy. The lesion is much smaller. The congestion of the conjunctival vessels and the corneal infiltration is much less.

Desensitization with tuberculin did not as a rule give results in lesions involving the conjunctiva.[3]

The present preferred treatment is the use of combinations of the following drugs because of their synergistic action in specifically destroying tubercle bacilli:[10] (a) streptomycin or dihydrostreptomycin; (b) para-aminosalicylic acid (PAS); (c) Isoniazid.

Woods[23] recommends a mixture of all three drugs be used for at least 42 days. Kratka[10] suggested that two or three months of therapy are necessary for satisfactory clinical results.

Report of a case

The patient, A. D., a 36-year-old Puerto Rican male was first seen at the New York Eye and Ear Infirmary on June 6, 1958, complaining of redness of the right eye for two months' duration. This eye was also occasionally tender. He had been unsuccessfully treated elsewhere.

Ocular examination. Visual acuity was: O.D., 20/30-1; O.S., 20/30. There was plus-four conjunctival injection with an elevated, circumscribed pink lesion at the 11 o'clock position near the limbus of the right eye (fig. 1). A slight mucoid discharge was present. The cornea, anterior chamber, iris,

Fig. 3 (Anhalt, Zavell, Chang and Byron). A photograph to show that the ocular lesion has almost disappeared. This photograph was taken on September 17, 1958, after 19 days of therapy.

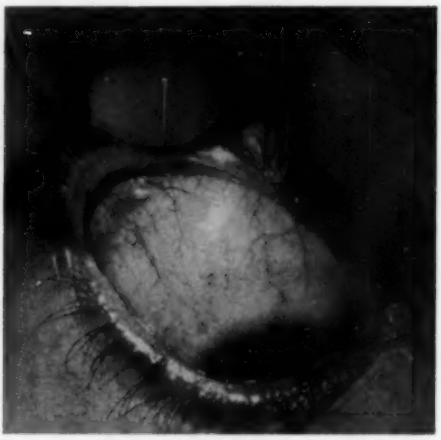

Fig. 4 (Anhalt, Zavell, Chang and Byron). A photograph taken on December 5, 1958, to show the right eye after therapy. No evidence of the ocular lesion remains.

lens media and fundi were negative. The diagnosis at this time was episcleritis, O.D. The patient was given steroid drops for local use.

The patient did not return until August 27, 1958. The size of the lesion had increased threefold and measured 8.0 mm. by 2.0 cm. The appearance was that of a yellowish-red mass infiltrated with a translucent, gelatinous material. There was fine vascularization on the surface of the lesion. The conjunctival vessels were engorged and the palpebral conjunctiva was edematous and congested. The cornea showed slight limbal infiltration. The lacrimal gland was intensely hyperemic and granular-like in appearance, containing multiple yellowish white foci beneath the epithelium.

The patient was admitted to hospital on August 29, 1958.

Physical examination revealed, in addition to the ocular lesion, the presence of a preauricular, two cervical and one axillary lymph nodes on the right side. The remainder of the physical examination was negative.

Bacteriologic examination. Scrapings from the ocular lesion were inoculated onto normal human tonsil epithelial cells in tissue culture.[8] Acid-fast bacilli were found growing in these cultures, with typical cord formation indicative of a virulent strain of tubercle bacillus[10] (fig. 6). Cultures of sputum and gastric washings on Löwenstein-Jensen media were negative.

Biopsy was refused by the patient.

Skin tests. The skin tests for lymphogranuloma venereum and brucellosis were negative. Mantoux, 1:100,000 showed a plus-four reaction. This consisted of induration measuring two by two inches with erythema measuring three by four and one-half inches. The erythema extended along the medial surface of the forearm almost to the axilla (fig. 5).

Laboratory tests. The blood, agglutination tests, blood sugar, urine and Wassermann were negative.

X-ray studies. The X-ray films of the chest and teeth were negative. There was slight cloudiness of the left frontal sinus.

Treatment. Treatment, started on August 29, 1958, consisted of Isoniazid 300 mg. daily and dihydrostreptomycin, one gm. three times per week. Figure 2 shows results after five days of therapy. This therapy was continued until September 8, 1958, when the patient was discharged on Isoniazid (400 mg. daily and PAS 10 gm. daily). Figure 3 shows the ocular lesion on the day prior to discharge.

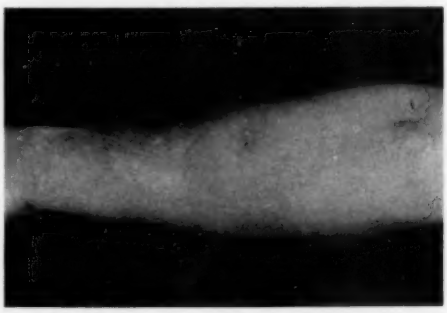

Fig. 5 (Anhalt, Zavell, Chang and Byron). A photograph to show the reaction of the Mantoux skin test, 1:100,000. The area of induration measured 2.0 by 2.0 inches. The area of erythema measured 3.0 by 4.5 inches.

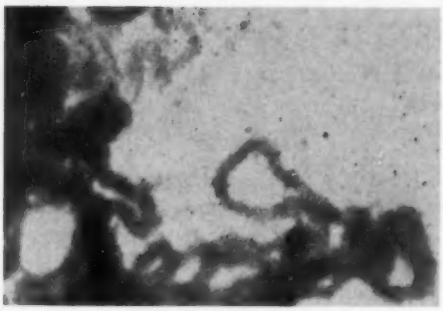

Fig. 6 (Anhalt, Zavell, Chang and Byron). A photomicrograph to show the typical cord formation of the Mycobacterium tuberculosis as grown on normal human tonsil epithelial cells in tissue culture. (Acid-fast stain, ×450).

Course. There was a marked regression of the original ocular lesion (fig. 1) on therapy. By September 8, 1958, the lacrimal gland appeared almost normal and by September 12th the ocular lesion had almost disappeared. On continued therapy the lesion disappeared entirely and the eye recovered its original normal appearance (fig. 4).

Summary

Conjunctival tuberculosis was reviewed from the viewpoints of its history, incidence, route of infection, clinical picture, clinical classification, diagnosis, differential diagnosis and treatment. A bacteriologically proven case of conjunctival tuberculosis successfully treated with streptomycin, PAS and Isoniazid was presented with photographs.

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References

1. Bruce, G. M., and Locatcher-Khorazo, D.: Primary tuberculosis of the conjunctiva. A.M.A. Arch. Ophth., **37**:375, 1947.
2. Donegan, J. M.: Primary tuberculosis of the conjunctiva. Am. J. Ophth., **33**:1117, 1950.
3. Duke-Elder, W. S.: Textbook of Ophthalmology. St. Louis, Mosby Company, 1938, v. 2, p. 1634.
4. Eadie, S.: Primary tuberculosis of the conjunctiva treated with streptomycin and PAS. Brit. J. Ophth., **38**:568, 1954.
5. Evans, A. S.: Establishment of human adult tonsil cells in continuous culture and their virus susceptibilities. Proc. Soc. Exper. Biol. & Med., **96**:752, 1957.
6. Eyre, J. N. H.: Tuberculosis of the conjunctiva. Lancet, **1**:1319, 1912.
7. Goldfarb, A. A., and Seltzer, I.: Primary tuberculosis of the conjunctiva. Am. J. Dis. Child., **72**: 211, 1956.
8. Juler, F.: Primary tuberculosis of the conjunctiva treated with streptomycin. Tr. Ophth. Soc. U. Kingdom, **69**:297, 1950.
9. Kamel, Sabri: Primary tuberculosis of the conjunctiva. Brit. J. Ophth., **34**:322, 1950.
10. Kratka, W. H.: Isoniazid and ocular tuberculosis: Evaluation of experimental and clinical studies. A.M.A. Arch. Ophth., **54**:330, 1955.
11. Merz, E. H., and Walsh, J. J.: Tuberculosis of external eye: Ill. Med. J., **113**:239, 1958.
12. McKenzie, W. H.: Tuberculosis of the conjunctiva. Am. J. Ophth., **22**:744, 1939.
13. McNicholas, P. J.: Primary tuberculous complex in the conjunctiva. Irish J.M. Sc., **308**:386, 1951.
14. Plucinski, K.: Primary tuberculous conjunctival ulcer. Tubercle, **33**:40, 58, 1952.
15. Ruggiero, H. R., Halperin, L., and Arouh, J.: Primo-infeccion tuberculosa conjunctival. Arch. oftal, Buenos Aires, **30**:485, 1955.
16. Sacca, M.: Tubercolosi primitiva della congiuntiva; presentazione di un caso. Minerva pediat., **6**: 460, 1954.
17. Samuelson, A.: Primary tuberculosis of the conjunctiva. A.M.A. Arch. Ophth., **15**:975, 1936.
18. Shepard, C. C.: Growth characteristics of tubercle bacilli and certain other mycobacteria in Hela cells. J. Exper. Med., **105**:39, 1957.
19. Sitchevska, O., and Sedam, M.: Primary tuberculosis of the conjunctiva. Arch. Ophth., **30**:196, 1943.
20. Starke, H.: Primare Bindehauttuberkulose. Klin. Monatsbl. f. Augenh., **114**:107, 1959.
21. Sykowski, P.: Conjunctival tuberculosis treated with streptomycin. Am. J. Ophth., **35**:1824, 1952.
22. Wheeler, J. R., and Sinclair, S. R.: Tuberculosis of the conjunctiva treated with (1) streptomycin and PAS, (2) Calciferol. Tr. Ophth. Soc. U. Kingdom, **72**:30, 1952.
23. Woods, A. C.: Pathogenesis and treatment of ocular tuberculosis. A.M.A. Arch. Ophth., **52**:174, 1954.

PHOSPHOLINE IODIDE (217MI) AND DEMECARIUM BROMIDE (BC48) IN THE MANAGEMENT OF GLAUCOMA*

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The ocular hypotensive effect of Phospholine Iodide has been reported on by Leopold, Gold and Gold[1] and its mechanism of action was studied by Becker, Pyle and Drews.[2] It was shown that it reduces the intraocular pressure by 48 percent in glaucomatous eyes and increases the facility of outflow by 120 percent (Drance[3]). Krishna and Leopold[4] discussed the long-term application of this drug to the management of glaucoma. Demecarium Bromide was known to have a powerful ocular hypotensive effect described by Gittler and Pillat[5] and it was shown to reduce intraocular pressure by 50 percent in glaucomatous eyes and to increase the facility of outflow by 120 percent (Drance[6]).

These drugs are powerful cholinesterase inhibitors which are water soluble and therefore obviate the disadvantages of DFP which has to be dissolved in fats. Demecarium Bromide is stable at room temperature whereas Phospholine Iodide has to be refrigerated at 4°C., as it loses its potency after three weeks at room temperature.

The present study was undertaken to evaluate the use of these drugs in the therapy of chronic simple and aphakic glaucoma. These drugs have been in use at this clinic for over 18 months but in view of the usual progressive nature of the disease a six-month period following stabilization was chosen for this follow-up report, in order to minimize the effect of the increased severity of the pathologic process as the cause of failure of control.

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Present study

The 65 eyes reported on were suffering from chronic simple glaucoma or open-angle aphakic glaucoma. Most of the patients were treated with conventional antiglaucoma therapy prior to the commencement of the present study, but failure of control of the glaucomatous process or sensitivity to the therapy employed necessitated a change of regime.

All patients were stabilized in the hospital and stabilization was considered adequate if the intraocular pressures remained below 25 mm. Hg throughout the 24 hours of the day and night. Attempts were made to normalize the outflow facility of the eyes, as far as possible. Intraocular pressures recorded on the ward were taken with the Schiøtz tonometer and the 1955 calibration scale was employed. The patients were discharged on the cholinesterase inhibitor with which they were stabilized and were followed at frequent intervals in the glaucoma clinic, where their intraocular pressures were checked both with the Schiøtz and the applanation tonometers. Visual fields were recorded and tonography was carried out with the Mueller electronic tonometer and Honeywell-Brown recorder. Tonographies were corrected for scleral rigidity where necessary.

Thirty-five eyes were treated with Phospholine Iodide (0.1 percent or 0.25 percent) daily or twice daily and 30 eyes were treated with Demecarium Bromide (0.25 percent) daily or twice a day. Patients whose control was inadequate were re-stabilized in the hospital by adding a carbonic anhydrase inhibitor and/or two-percent adrenalin to the regime.

Definition of control

Cases were considered controlled throughout the period of six months if after stabilization, around the clock, no field changes

took place, no changes occurred in the appearance of the optic nervehead and the intraocular pressure (applanation) remained below 25 mm. Hg. Tonographic data were analyzed in all cases but, even though adequate facility of outflow was aimed at, this was not considered essential in terms of control in this study.

Results

A. Phospholine Iodide (table 1)

Of the 35 eyes reported on in this study two eyes had to be excluded because on instillation of Phospholine Iodide the patient got an immediate generalized reaction. In the remaining 33 eyes which have been treated for periods from six to 18 months (table 3), 18 (55 percent) were considered to be controlled and 15 (45 percent) were considered not to be controlled under the criteria described.

Visual fields. Twenty-one (64 percent) eyes showed no change during the six months, seven (21 percent) deteriorated and five (15 percent) could not be plotted due to the low vision in the eye or the patient's poor co-operation. In the seven eyes whose fields had deteriorated (table 4), three had raised intraocular pressures, two others had very low coefficients of outflow and in one other the fraction Po/C was over 100.

Intraocular pressures. Twenty-two (67 percent) of the 33 eyes showed consistently satisfactory intraocular pressures whereas 11 (33 percent) showed pressures over 25 mm. Hg during the six-month study. With the addition of carbonic anhydrase inhibitor the intraocular pressure of 26 eyes (79 percent) was adequately controlled. Of the seven eyes which showed raised pressures (table 5), four showed no change in the visual fields, two showed deterioration of the visual field while one could not be plotted.

Tonography. Eighteen (55 percent) eyes showed a coefficient of outflow of 0.15 c. mm. per minute per mm. Hg or more, 13 showed a coefficient of outflow of 0.10 to 0.14 and two showed a coefficient of outflow of less than 0.10. The tonographic findings during the six month follow-up compared with those obtained during stabilization in the hospital (table 6) show that in 13 of the eyes the coefficient of outflow deteriorated by 30 percent or more; in 13 the coefficient of outflow remained more or less unchanged and four showed a better coefficient of outflow by 30 percent or more.

B. Demecarium Bromide (table 2).

Of the 30 eyes under study, two had to be excluded because the drops were discontinued after a month due to pain. In the remaining 28 eyes 18 (64 percent) were controlled as defined (table 3); 10 (36 percent) were not controlled.

Visual fields remained unchanged in 14 eyes, (50 percent), deteriorated in five eyes (18 percent) and could not be plotted in nine eyes (32 percent). Of the five eyes whose fields had deteriorated (table 4), three had raised intraocular pressures and inadequate coefficients of outflow.

Intraocular pressure remained under 25 mm. Hg throughout the six months in 15 (56 percent); 13 (44 percent) eyes showed intraocular pressures over 25 mm. Hg. With the addition of a carbonic anhydrase inhibitor 22 eyes (78 percent) were adequately controlled with regard to the intraocular pressure. In the six eyes with raised intraocular pressures (table 5), three eyes showed deterioration of the visual fields, one showed no change in the visual field, and two could not be plotted.

Tonography. The coefficient of outflow was 0.15 or over in 15 (57 percent) of eyes; between 0.1 and 0.14 in six (21 percent) of the eyes and less than 0.1 in five (17 percent) of eyes. Comparing the tonography during the six month period of study with the tonography attained during the period of stabilization in hospital it appears that in seven eyes the coefficient of outflow deteriorated by 30 percent or more, in five eyes the coefficient of outflow improved by 30 percent and in 14

TABLE 1

THIRTY-FIVE GLAUCOMATOUS EYES TREATED WITH PHOSPHOLINE IODINE

No.	Diagnosis	Months of Therapy	Vision		Visual Field	Intraocular Pressure		Tonography		Medication
			Before	After 6 mo.		Office Range	Hosp. Stabilization	Office	Hosp. Stabilization	
1. OD OS	Chronic simple Chronic simple	18 18	20/15 20/30	20/25 20/40	Unchanged Unchanged	18–20 20–21	21 21	0.13 0.13		1. 0.1% bid 2. 0.25% daily + carb. anhy. inhibitor
2. OD OS	Chronic simple Chronic simple	6 6	PL 20/25	PL 20/400	Not plottable Deteriorated	18–20 21–28	18 21	0.14 0.15	0.15 0.17	1. 0.25% daily 2. 0.25% bid + carb. anhy. inhibitor
3. OD OS	Aphakia Aphakia	14 14	20/40 20/400	20/25 20/400	Unchanged Not plottable	34 44	10 11	0.11 0.11	0.33 0.28	1. 0.1% daily
4. OD OS	Chronic simple Chronic simple	12 12	20/20 20/20	20/20 20/20	Unchanged Unchanged	23–38 24–30	17 16	0.11 0.13	0.27 0.26	1. 0.1% × 2 2. 0.25% × 1 3. 0.25% × 2
5. OS	Chronic simple	11	20/25	20/25	Unchanged	18–22	17	0.17	0.19	1. 0.1% daily 2. 0.25% daily
6. OD OS	Chronic simple Chronic simple	12 12	20/20 CF	20/20 CF	Unchanged Not plottable	16 16	12 13	0.17 0.13	0.25 0.25	1. 0.25% daily
7. OD OS	Chronic simple Chronic simple	6 6	CF 20/25	CF 20/30	Not plottable Deteriorated	14–18 17–18	10 11	0.18 0.14	0.31 0.24	1. 0.25% daily
8. OD	Chronic simple	7 87	20/20	20/20	Deteriorated	18.5	17	0.13		1. 0.1% daily 2. 0.25% daily
9. OD OS	Chronic simple Chronic simple	12 12	20/20 20/20	20/20 20/20	Unchanged Unchanged	13–21 11–19	12 14	0.22 0.28	0.24 0.20	1. 0.1%
10. OD OS	Chronic simple Chronic simple	9 9	20/200 20/20	20/70 20/20	Unchanged Unchanged	20–26 17–23	21 15	0.16 0.15	0.17 0.19	1. 0.25% daily
11. OD OS	Chronic simple Chronic simple	9 9	PL 20/20	PL 20/30	Not plottable Unchanged	13–21 13–16	15 18	0.15 0.13	0.09 0.14	1. 0.25% daily
12. OD OS	Chronic simple Chronic simple	7 7	20/20 20/20	20/20 20/20	Unchanged Unchanged	22–24 22–27	12 16	0.16 0.13	0.13 0.13	1. 0.25% bid
13. OD OS	Chronic simple Chronic simple	6 6	20/50 20/50	20/50 20/60	Unchanged Unchanged	14–16 13–18	10 12	0.16 0.17	0.23 0.29	1. 0.25% daily
14. OD OS	Chronic simple Chronic simple	6 6	20/20 20/20	20/25 20/25	Unchanged Unchanged	17–19 17–19	13 16	0.13 0.10	0.19 0.18	1. 0.25% daily 2. 0.25% daily
15. OD	Chronic simple	1 hr.								Immediate reaction—Tremor, Headache bradycardia, hypotension, abdominal pain
16. OD OS	Chronic simple Chronic simple	6 6	20/70 20/25	20/400 20/30	Deteriorated Deteriorated	16–18 16–18	14 16	0.19 0.16	0.17 0.19	1. 0.25% bid Macular disease
17. OD OS	Chronic simple Chronic simple	4 4	20/20 20/20	20/30 20/30	Deteriorated Deteriorated	20–32 17–26	20 15	0.90 0.17	0.15 0.17	1. 0.25% daily 2. 0.25% bid operation
18. OD	Chronic simple	6	20/25	20/20	Unchanged	21–25	16	0.19	0.22	1. 0.25% daily + carb. anhy. inhib.
19. OD OS	Chronic simple Chronic simple	10 10	20/25 20/30	20/70 20/30	Unchanged Unchanged	19–28 23–32	16 17	0.22 0.20	0.14 0.15	1. 0.1% daily 2. 0.25% bid + adrenalin 2% + carb. anhy. inhib.

TABLE 2

THIRTY GLAUCOMATOUS EYES TREATED WITH DEMECARIUM BROMIDE

No.	Diagnosis	Months of Therapy	Vision		Visual Field	Intraocular Pressure		Tonography		Medication
			Before	After 6 mo.		Office Range	Hosp. Stabilization	Office	Hosp. Stabilization	
1. OD	Aphakia	6	20/25	20/20	No damage	16–24	12	0.23	0.28	1. 0.25% daily
OS	Chronic simple	6	PL	PL	Not plottable	15–34	11	0.09	0.21	2. 0.25% ×2
2. OD	Chronic simple	7	20/200	20/200	No damage	29–34	9	0.13	0.18	1. 0.1% daily
OS	Chronic simple	7	20/20	20/20	No damage	20–25	8	0.11	0.29	2. 0.25% daily 3. 0.25% bid
3. OD	Chronic simple	7	20/25	20/25	Deteriorated	18–21	21	0.19	0.31	1. 0.25% daily
OS	Chronic simple	7	20/50	20/50	Deteriorated	18	17.5	0.18	0.20	2. 0.25% bid
4. OD	Chronic simple	6	20/50	20/50	Unchanged	15	16	0.26	0.16	1. 0.25% daily
5. OD	Chronic simple	6	20/50	20/50	Unchanged	18–30	17	0.13	0.12	1. 0.25% daily
OS	Chronic simple	6	20/40	20/40	Deteriorated	20–36	19	0.19	0.14	
6. OD	Chronic simple	6	PL	PL	Not plottable	17–23	17	0.11	0.11	1. 0.25% bid
OS	Chronic simple	6	20/400	20/400	Unchanged	20–23	17	0.23	0.21	2. 0.5% daily
7. OD	Chronic simple	1	Stopped Because of Pain							
OS	Chronic siiple	1								
8. OD	Aphakia	6	20/20	20/20	Unchanged	7–8	7	0.18	0.23	1. 0.25% daily
OS	Aphakia	6	PL	PL	Not plottable	16.5	12	0.09	0.14	
9. OD	Chronic simple	6	20/40	20/40	Unchanged	56	16	0.04	0.13	1. 0.25% ×2
OS	Chronic simple	6	20/40	20/20	Unchanged	54	15	0.03	0.12	
10. OD	Chronic simple	12	20/30	20/25	Deteriorated	15–30	11	0.13	0.20	1. 0.1% bid
OS	Chronic simple	12	20/40	20/30	Deteriorated	15–25	13	0.18	0.20	2. 0.25% daily 3. 0.25% bid
11. OD	Chronic simple	8	20/20	20/25	Unchanged	21–25	14	0.19	0.19	1. 0.1% daily
OS										2. 0.25% daily
12. OS	Chronic simple	6	20/70	20/50	Unchanged	15–17	12	0.16	0.20	1. 0.1% daily and carb. anhy. inhibitor
13. OD	Aphakia	8	20/200	20/200	Not plottable	20–26	12	0.12	0.21	1. 0.25% daily +adrenaline 2% daily
OS	Aphakia	8	20/50	20/40	Not plottable	20–22	12	0.47	0.24	
14. OD	Chronic simple	8	20/40	20/30	Unchanged	29–30	20	0.11	0.09	1. 0.1% daily 2. 0.25% daily 3. 0.25% bid +carb. anhy. inhibitor
15. OD	Chronic simple	6	PL	PL	Not plottable	21–31	22	0.09	0.11	1. 0.25% daily
OS	Chronic simple	6	20/30	20/30	Unchanged	16–27	13	0.17	0.15	2. 0.5% daily 3. 0.25% daily +carb. anhy. inhibitor
16. OD	Aphakia	6	20/400	20/400	Not plottable	37	21		0.11	1. 0.25% daily
OS	Chronic simple	6	20/40	20/30	Not plottable	27	18		0.15	2. 0.25% bid 3. 0.25% bid +carb. anhy. inhibitor
17. OD	Chronic simple	6	CF	CF	Not plottable	16–23	10	0.31	0.19	1. 0.25% daily
OS	Chronic simple	6	20/30	20/30	Unchanged	18–25	12	0.24	0.16	

TABLE 3

THE STATE OF CONTROL OF GLAUCOMATOUS EYES WITH CHOLINESTERASE INHIBITORS

	Phospholine Iodide	Demecarium Bromide	Total
Number of eyes studied	33	28	61
Controlled	18 (55%)	18 (64%)	36 (59%)
Not controlled	15 (45%)	10 (36%)	25 (41%)
Controlled with addition of carbonic anhydrase inhibitor	26 (79%)	22 (78%)	48 (78%)
Visual fields			
Unchanged	21 (64%)	14 (50%)	35 (58%)
Deteriorated	7 (21%)	5 (18%)	12 (20%)
Not obtainable	5 (15%)	9 (32%)	14 (22%)
Intraocular pressure			
Under 25 mm. Hg	22 (67%)	15 (56%)	37 (60%)
Over 25 mm. Hg	11 (33%)	13 (44%)	24 (40%)
Tonography			
>0.15	18 (55%)	15 (57%)	33 (54%)
0.1–0.14	13 (39%)	6 (21%)	19 (31%)
<0.1	2 (6%)	5 (17%)	7 (15%)

TABLE 4

STATUS OF CONTROL OF EYES WITH FIELD DETERIORATION

	Phospholine Iodide	Demecarium Bromide	Total
Number with field deterioration	7	5	12
Raised intraocular pressure and poor coefficient of outflow	3	3	6
Decreased coefficient of outflow only	2	—	2

TABLE 5

STATUS OF VISUAL FIELDS IN PATIENTS WITH UNCONTROLLED INTRAOCULAR PRESSURE

	Phospholine Iodide	Demecarium Bromide	Total
Number with raised pressure	7	6	13
Unchanged visual fields	4	1	5
Deterioration of fields	2	3	5
Not obtainable	1	2	3

eyes it remained unchanged. The tonographic findings during the period of initial stabilization were compared with those found during

TABLE 6

STATUS OF COEFFICIENT OF OUTFLOW DURING STUDY AS COMPARED TO STABILIZATION

Coefficient of Outflow	Phospholine Iodide	Demecarium Bromide	Total
Deteriorated 30% or more during	13	7	20
Improved 30% or more	4	5	9
Unchanged	13	14	27

the six-month follow-up (table 6). In seven eyes the coefficient of outflow deteriorated by 30 percent or more; 14 eyes showed no change, whereas five eyes showed improvement of the coefficient of outflow by 30 percent or more.

It is also interesting to note that the majority of eyes controlled on Phospholine Iodide or Demecarium Bromide required stronger concentration or more frequent administration of drops than was required for the original stabilization.

SIDE-EFFECTS

Early in the present study in about 10 eyes the therapy had to be discontinued because of fairly severe pain or visual deterio-

ration due to miotic pupils in eyes with considerable lens opacities. Familiarity with the action of the drugs made indications for discontinuation very much less frequent. The visual impairment due to miosis can be counteracted by the use of 10-percent Neosynephrine two or three times a day which dilates the pupil but does not seem to interfere with the maintenance of pressure control in the eye. Discomfort is also bearable in the majority of the patients as they can be reassured that it will pass off after the first few days.

The side-effects noted were:

1. Pain in the eye and over the brow.
2. Conjunctival congestion and lacrimation.
3. Visual disturbance due to ciliary spasm and an induced myopia. One eye of a volunteer who had one drop of Demecarium Bromide instilled during the initial period of study showed an exudative iridocyclitis which subsided very promptly on discontinuation of therapy and instillation of topical steroids.
4. Disturbance of vision due to the extreme miosis in patients with lens opacities.
5. One patient on Phospholine Iodide had an immediate generalized disturbance with abdominal pain, diarrhea, bradycardia, low blood pressure, tremors, generalized weakness and headache. This was counteracted by a subcutaneous injection of atropine sulfate. In the present series no retinal detachments due to the therapy were noted nor were any iris cysts seen.

Plasma and red blood cell cholinesterase and pseudocholinesterase levels were carried out and these were found to be considerably depressed in most of the patients on prolonged therapy; however, as none of these patients showed systemic side-effects it appears obvious that the drugs do not seem to penetrate the blood brain barrier and do not produce any central nervous system upset. The study of the cholinesterase level will form the subject of a separate communication.

Comment

The long acting powerful cholinesterase inhibitors, Phospholine Iodide and Demecarium Bromide, seem to have advantages in the treatment of chronic simple glaucoma and aphakic glaucoma over the miotics previously described. The main advantages of the drugs are:

1. Infrequency of instillation required to control intraocular pressure.
2. Increase in the coefficient of aqueous outflow which normalizes the intraocular dynamics.
3. The water solubility of these drugs as opposed to the lipoid solubility of DFP.
4. The control of cases of chronic simple glaucoma which had previously failed to be controlled by standard antiglaucomatous therapy of conservative nature.
5. The lack of penetration of the drugs through the blood-brain barrier which makes them very much safer than DFP.

It is felt that these drugs should not be included in the management of angle-closure glaucoma as it has been felt that with subacute angle-closure glaucoma the outflow facility may be impaired and an acute attack may be induced.

Summary

The use of the strong, long-acting, water-soluble cholinesterase inhibitors, Phospholine Iodide and Demecarium Bromide, in the management of chronic simple glaucoma is evaluated over periods from six to 18 months. Of eyes treated, 79-percent could be controlled with the drugs themselves or in conjunction with such other drugs as carbonic anhydrase inhibitors or adrenalin. The side-effects and their management are discussed.

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References

1. Leopold, I. H., Gold, P., and Gold, D.: Use of 217 MI in treatment of glaucoma. A.M.A. Arch. Ophth., **58**:363, 1957.
2. Becker, B., Pyle, G. C., and Drews, R.: The effect of Phospholine Iodide on aqueous outflow. Am. J. Ophth., **45**:929, 1958.
3. Drance, S. M.: The effects of Phospholine Iodide on the intraocular pressure in man. Am. J. Ophth., to be published.
4. Krishna, N., and Leopold, I. H.: Glaucoma: Echothioplate iodide therapy. A.M.A. Arch. Ophth., **62**: 300, 1959.
5. Gittler, R., and Pillat, B.: Die Verwendung von Demecarium Bromide bei der Therapie des Glaukoms. Arch. f. Ophth., **157**:473, 1956.
6. Drance, S. M.: The effect of demecarium Bromide on the intraocular pressure in man. A.M.A. Arch. Ophth., **62**:673, 1959.

COMPARATIVE BEHAVIOR OF RESPIRATORY, CONJUNCTIVAL, AND CORNEAL EPITHELIUM*

In the anterior chamber in cats and dogs

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Attempts to promote invasion of the anterior chamber by corneal epithelium, through various types of penetrating corneal defects, were described in a previous paper.[1] In no instance, with any of the methods used, did invasion (downgrowth) occur. Migration of epithelium took place promptly after penetrating wounds were made but, before it could reach the anterior chamber, its path was invariably blocked by a fibrin barrier that formed quickly and closed the defect as far as the migrating epithelium was concerned.

In the present paper, results of various epithelial transplants into the anterior chamber are reported.

The anterior chamber has long been used as a site for in vivo tissue culture. Many types of tissue, including some that are malignant, have been transplanted. Some workers also have studied the growth of corneal and conjunctival epithelium, both clinically and experimentally,[2–4] and some have used nasal epithelium.[5] In general, epithelium does not grow well in the anterior chamber and one cannot help wondering if there is a specific inhibitor in the aqueous directed against the corneal and conjunctival epithelium, or, if the aqueous is just a poor culture medium. The previous study did not answer this question because the epithelium did not actually gain access to the anterior chamber.

A difference of opinion seems to exist as to the nutritive qualities of the aqueous. Some have used it as one ingredient in culture media as a nutrient, while others have found that it has an inhibitory action.[6] In vivo and in vitro, it may act differently. Primary aqueous withdrawn from the living eye and used in vitro is quite different chemically from the secondary aqueous in which a transplant in vivo is first bathed.

Several types of transplants were used in the present studies. Among others, a foreign epithelium was compared with ocular epithelium to see if, perchance, a difference in growth might be revealed that would throw some light on the question of a specific inhibitor. Respiratory epithelium from the sinus was selected because it is a rudimentary type of structure, grows readily, it

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is easily obtainable, and is, for practical purposes, sterile.

Material and Technique

The experimental animals used were dogs and cats.

The technique was simple. Through a keratome incision, the various transplants were introduced into the anterior chamber and moved as far away from the incision as possible. When two transplants were inserted, the incision was made above and a transplant placed low down on each side. Despite these precautions, the transplants not infrequently became adherent to the incision.

To obtain the respiratory epithelium, the scalp over one frontal sinus was incised and reflected and a window made through the bone either by chisel and rongeur or by dental burr and rongeur. As soon as the bone was penetrated, while the mucoperiosteum was still intact, wet cotton packing was gently inserted into the sinus to separate the mucoperiosteum from the bone. In this way, tearing of the delicate tissue can be largely avoided. When a sufficient area (6.0 to 8.0 mm. square) had been exposed, the mucoperiosteum was grasped with a fine eye forceps, such as a Kalt, a generous piece excised and promptly transplanted into the anterior chamber.

The conjunctival epithelium was usually taken immediately above the cornea and, on a few occasions, from the nictitating membrane. Corneal epithelium was obtained by scraping the cornea, or making a through and through trephine opening in one eye and transplanting the button.

Study I: Corneal scrapings (Experiments 1 through 8)

The corneas of eight eyes were firmly scraped with a Curdy keratome and the scrapings picked up in a syringe by sweeping the bevel of a fine needle over the surface. The scrapings were then injected into the anterior chamber of the same or fellow eye, and, in one instance, into both. The results can be given in two words—nothing happened. None of the eyes showed any clouding of the anterior chamber nor did any develop a significant inflammatory reaction. There were neither free floating nor growing epithelial cells in any of the eyes examined histologically.

Study II: Transplantation of trephine buttons (Experiments 9 through 20)

This procedure was carried out on 12 different eyes. A two-mm. full-thickness trephine button was obtained from one cornea and transplanted into the anterior of the same or fellow eye. The animals were killed from six hours to 147 days after operation. The results are given in Table 1. In none did the epithelium appear to grow. In the three-day eye it split and formed a kind of cyst in which were found swollen, rounded, desquamated epithelial cells. (fig. 1). In the six-day eye, the epithelium was inverted to form a cyst and was buried in new fibrous tissue. The cavity was filled with loose cells in various stages of degeneration. (fig. 2) After 21 days, the buttons had all disappeared. The stroma seemed to last somewhat longer than the epithelium.

In none of these eyes was there even a suggestion of an outgrowth of epithelium from the corneal transplant.

Study III: Conjunctival transplants (Experiments 21 through 34)

Fourteen conjunctival transplants were made into the anterior chamber in 12 cats. Four transplants were taken from the nictitating membrane and 10 from the bulbar conjunctiva. Eleven cats were killed from six hours to 442 days following operation. The other cat upon which three experiments were done is still living (table 2).

In this study, of 14 conjunctival transplants, seven disappeared and seven were present, five in the form of small nodules, the sixth in the form of a small cyst and the

TABLE 1

TRANSPLANTED TREPHINE BUTTONS (STUDY II)

Experiment No.	Killed Postoperatively	Transplant Button Found Postmortem	Histologic Findings
9	6 hr.	Yes	Epithelium normal. Stroma swollen. No nuclear proliferation
10	3 da.	Yes	Epithelium splitting into two layers between which are loose, swollen, detached cells, some with swollen and some pyknotic nuclei. Stroma swollen. No nuclear proliferation (fig. 1)
11	6 da.	Yes	Entire button surrounded by fibrin, new fibrous connective tissue and fibroblasts. Epithelium buried under this and has formed cyst filled with loose epithelial cells. These are swollen, have pyknotic nuclei. Cells in basal layers on outside of cyst appear normal (fig. 2)
12	10 da.	Yes	Button buried in iris excepting small stem. Only small bit of epithelium found lying against iris. Cells about normal. Proliferation of corneal stromal cells questionable
13	12 da.	Yes	Button grafted into the incision and healing in. No epithelium found excepting that on the anterior corneal surface
14	20 da.	No*	
15	21 da.	Yes	Button buried in iris stroma. Few epithelial cells in center. Stromal fibers swollen. Nuclei swollen and faintly stained or pyknotic
16	24 da.	No	
17	40 da.	No	
18	80 da.	No†	
19	87 da.	No‡	
20	147 da.	No‡	

* Anesthetized on 13th postoperative day and button (transplant) could not be found.

† Pigment spot found in angle by corneal microscope and histologically. May have been remnant of transplant. Not recognizable.

‡ Anterior iris adhesion found.

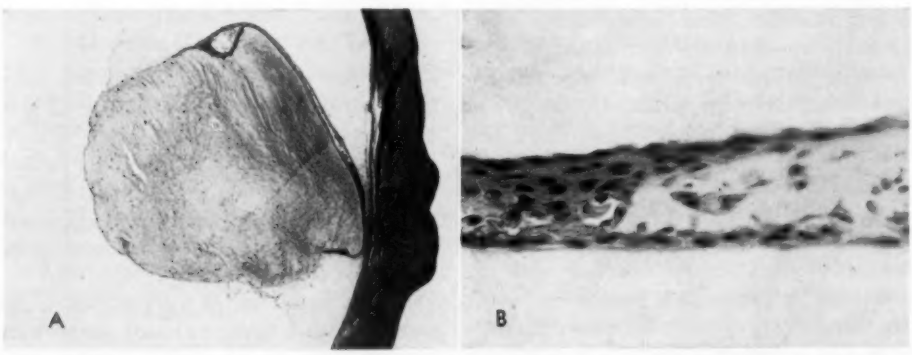

Fig. 1 (Hilding). Trephine button after three days within the anterior chamber. (A) The epithelium seems to be splitting to form a cyst. (B) Higher power of the splitting epithelium.

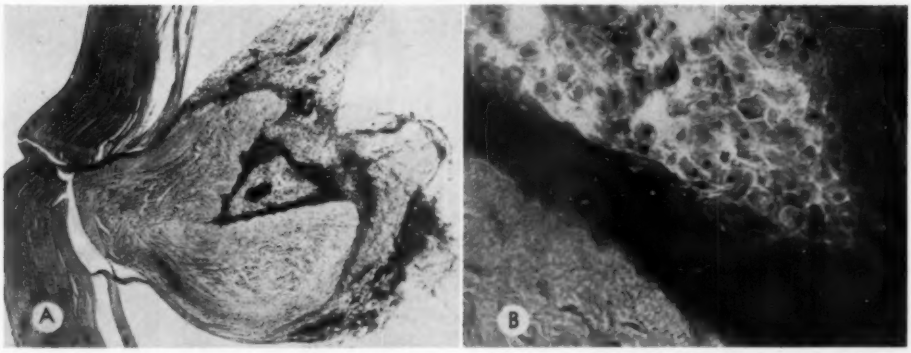

Fig. 2 (Hilding). Trephine button after six days in anterior chamber. (A) The epithelium has inverted to form a cyst and is buried in fibrous tissue. The basal cells are outside and the desquamating surface cells inside. (B) Higher magnification showing desquamating cells within the cyst.

TABLE 2

NICTITATING MEMBRANE AND BULBAR CONJUNCTIVA (STUDY III)

Experiment No.	Time after Operation	Transplant Present	Findings	
			Gross or Slitlamp	Histologic
21	6 hr.	Yes	No change	No change
22	6 da.	No	May have been extruded	
23	10 da.	No	May have been extruded	Not found in serial sections
24	21 da.	Yes	Enclosed in fibrin	Small fibrous mass attached to cornea, partly surrounded by flat epithelium which is reduplicated to form a tiny flat cyst (fig. 3)
25	32 da.	Yes	Small nodule 1 mm. in diameter attached to incision	Fibrous mass attached to cornea, partly covered by modified mucus-producing squamous epithelium (fig. 4)
26	40 da.	No		
27	114 da.*†	No		
28	274 da.	Yes	2 mm. white nodule attached to pupillary margin	Fibrous mass covered by regular conjunctiva. epithelium. Many cells mucus-containingl Good blood supply from iris. Outgrowth for 0.25–0.50 mm. on iris (fig. 5)
29	442 da.‡	No		
30	370 da.	Yes	1 mm. pigmented nodule on iris	
31	305 da	No	Absorbed—nothing seen	
32	282 da.	No	Gone	
33	440 da.†	Yes	Flat 3 mm. cyst in corneal stroma	
34	440 da.†	Yes	1.5 mm. pearl on posterior corneal surface at incision. Apron 1–2 mm. wide	

* Gone on gross examination in living animal at 55 days. † Animal still living.
‡ Gone on gross examination in living animal at 27 days.

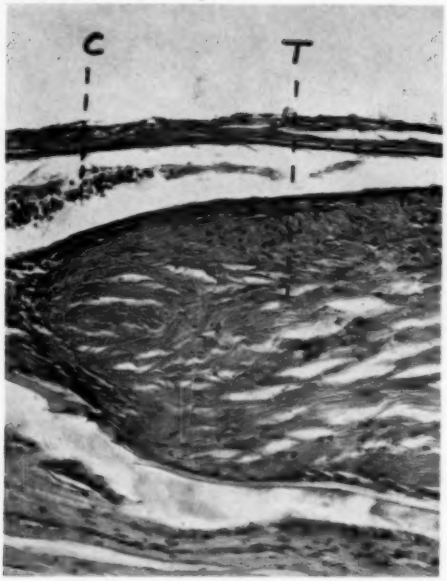

Fig. 3 (Hilding). Twenty-one day conjunctival transplant (T), showing a tiny cyst (C).

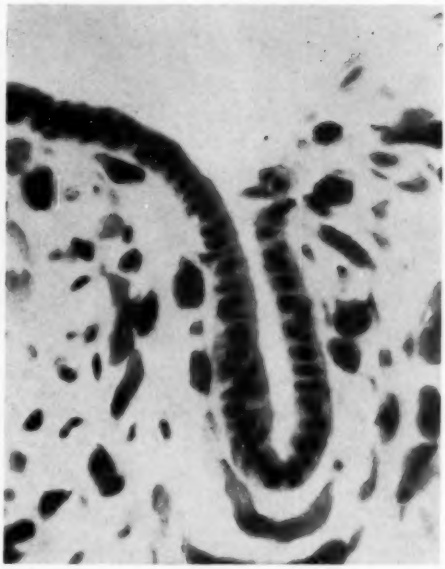

Fig. 5 (Hilding). End of outgrowth (conjunctival) upon iris. It ends quite abruptly in three irregular cells.

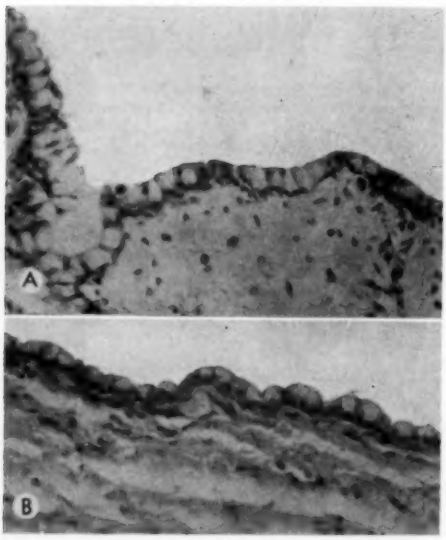

Fig. 4 (Hilding). (A) Thirty-two day conjunctival transplant, showing mucus-producing epithelial cells. (B) Similar cells in conjunctiva in situ on outside of eye.

seventh had only been transplanted for six hours and had neither changed form nor established circulation. All of the transplants that survived were attached by a fibrous pedicle either to a vascularized corneal incision or to the iris, and some to the lens capsule as well. None was floating free or attached to nonvascularized areas only. Blood-containing capillaries were found in all of the surviving transplants on which histologic sections were obtained.

The epithelium covered the lamina propria of the original transplant completely and extended for varying distances out upon the fibrous pedicle and, in two instances, for short distances upon the host tissue as well. Upon its own lamina propria, it retained its original character, including mucus-producing cells, but changed character upon the new fibrous tissue and host tissue. These portions contained no mucus-producing cells and appeared thin and atrophic. There was little difference in appearance between the 32-day transplant and the 274-day one.

TABLE 3

FRONTAL SINUS EPITHELIUM ALONE (STUDY IV)

Experiment No.	Postoperative Time Lapse (da.)	Transplant Present	Findings	
			Gross or Slitlamp	Histologic
35	147	Yes	Flat scar only	Tiny cysts in cornea lined by ciliated epithelium
36	131	Yes	Irregular cyst originating at pupillary margin. Grew rather large	Large mass of loose connective tissue surrounded by normal ciliated respiratory epithelium (fig. 6)
37	274	Yes	Tiny pigmented mass < 1 mm. on anterior surface of iris in the angle	Small, spherical, papillomatous lesion with the epithelium largely infolded but bathed in aqueous. Epithelium is of normal ciliated sinus type. Lamina propria distinct from the iris tissue, but iris cells, both fibroblasts and pigment cells, extend part way around the nodule and the whole covered with iris endothelium, excepting where the sinus epithelium comes to the surface
38	370	No	At first made a dark nodule on medial cornea, that decreased progressively in size. Last seen as nodule on 101st day. After that only tiny pigmented scar	
39	442	No	Transplant gone after 27 days	
40	305	No	Transplant first formed a tiny reddish cyst suspended between pupillary margin and cornea. Decreased progressively in size Last seen as nodule on 147th day. Final residual—stretched out anterior synechia	
41	282	No	This transplant was never seen postoperatively. Gone by 5th day	
42	393	Yes	Transplant looked like tiny worm-like mass on anterior lens capsule. Slowly decreased in size until barely recognizable. Iris adhesions both to lens capsule and corneal scar. Outgrowth on lens capsule (fig. 7)	Small connective tissue mass lying on anterior lens capsule, covered with respiratory epithelium and supplied with capillaries from iris. Epithelium is normal ciliated sinus type on the mass but it extends for a short distance (1 mm.) out on lens capsule. Here it looks like alveolar endothelium. (fig. 8)
43	440*	Yes?	Tiny, flat, elevated corneal lesion, 3 mm. in diameter. Could be cyst in stroma	

* Animal still living.

STUDY IV: FRONTAL SINUS EPITHELIUM
(Experiments 35 through 43)

Nine experiments were done in eight eyes (two in one dog's eye and seven in as many cats' eyes), transplanting mucoperiosteum removed from the frontal sinus into the anterior chamber. Table 3 summarizes the results of these experiments.

Of the nine transplants, four disappeared and five persisted until death. Only one of these formed a cyst. The only outgrowth was upon the lens capsule and this had a radius

measuring up to one mm. after 393 days. The latter two warrant special comment.

The transplant that formed a cyst grew progressively larger until it practically filled the anterior chamber (cornea 16 mm. in diameter) by the 72nd day, then it receded until it was only 3.0 by 4.0 mm. when the animal was killed after 131 days. The central portion of the cornea was somewhat cloudy. Histologic examination revealed that this was not an epithelial-lined cyst, the epithelium lay upon the outside of the mass (fig. 6). The cloudiness of the cornea was found to be due to a thin fibrous layer on the posterior surface, continuous with the fibrous plug of the incision and covered by endothelium.

The epithelium of the transplant which showed outgrowth upon the lens capsule became metaplastic and changed its character progressively according to the nature of the tissue on which it was based; in other words, the character of the tissue on which the epithelium was based seemed to determine its morphology. This finding seemed especially significant (figs. 7 and 8).

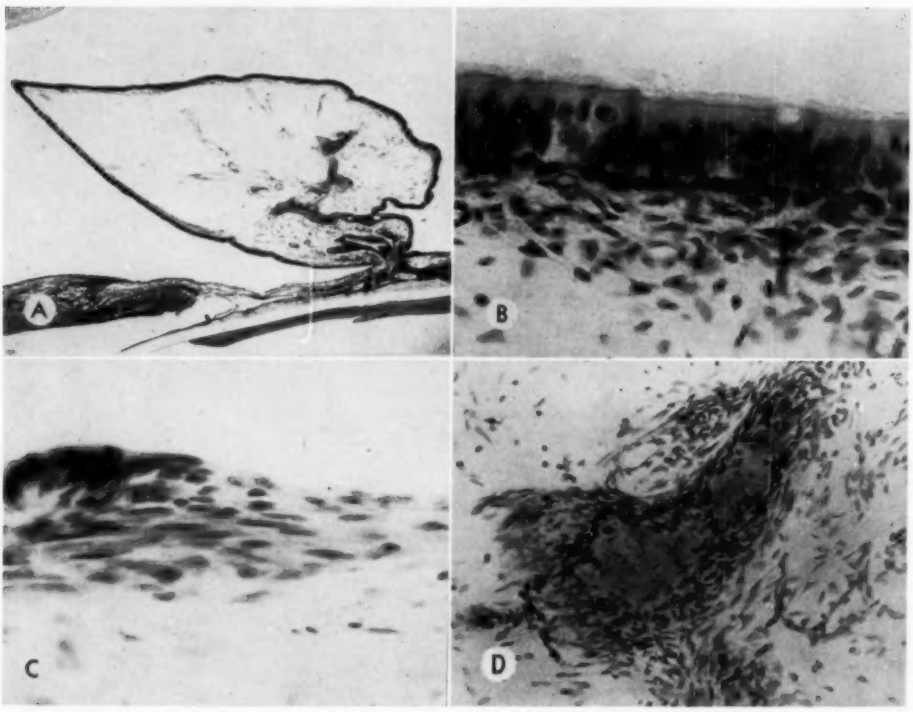

Fig. 6 (Hilding). (A) Experiment 36. Transplant of sinus mucoperiosteum after 131 days in anterior chamber. It forms a pedunculated mass engrafted upon the lens capsule and pupillary margin from which it draws its blood supply. A slender adhesion passed from its apex to the healed incision. It is covered on the outside by epithelium and consists otherwise of a capillary network supported by a loose connective tissue filled with large fluid spaces and containing growing bone and cartilage. The pedicle consists of dense, new fibrous tissue. (B) Normal appearing sinus mucosa after being bathed in aqueous 131 days. (C) Terminating margin of sinus epithelium on the fibrous pedicle. It does not grow well upon dense, new, fibrous tissue. It has changed its character and ends abruptly. (D) New bone growth within the transplant.

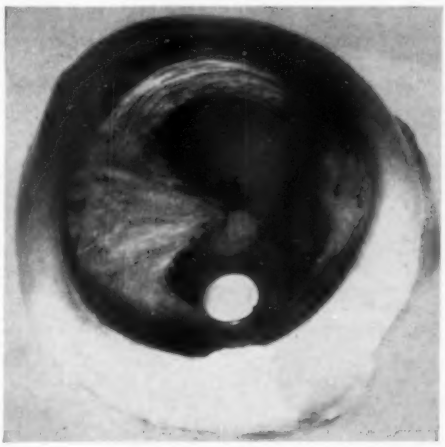

Fig. 7 (Hilding). Transplant of sinus mucoperiosteum after 393 days in anterior chamber. It is engrafted upon the anterior lens capsule and pupillary margin to which it is adherent and from which it drew blood supply. The epithelium is on the outside, bathed in aqueous but undoubtedly drawing nutrition from its own lamina propria. This transplant remained unchanged for many months and could be considered "healed."

Study V: Frontal sinus epithelium and conjunctiva transplanted together
(Experiments 44 through 54)

Frontal sinus epithelium and conjunctiva were transplanted together into the anterior chamber of four dogs' eyes and seven cats' eyes. The respiratory epithelium survived in six and disappeared in five. The conjunctival epithelium survived in seven and disappeared in four.

Of the four dogs' eyes, the sinus epithelium was found in three at histologic examination and the conjunctival epithelium in two (table 4). In all three of the respiratory transplants, the epithelium inverted to form cysts. In one, the cysts opened to the surface so that the surface also was covered. The epithelium on the outside was atrophic, flattened and looked squamous. In both the surviving conjunctival transplants, the epithelium was on the outside. In none of the dogs was there an extension of epithelial growth over the cornea or iris.

Of the seven cats' eyes, both transplants survived in three, the conjunctiva only in two, and neither in two. The two in which conjunctiva only survived contained white pearl-like nodules attached to the corneal scar. One of those in which both survived also showed a pearl which proved to be conjunctival in origin. From all three of these pearls an apronlike outgrowth extended out upon the posterior corneal surface. One was small—only 1.5 mm. from the transplant to margin of apron; the other two were larger —up to 7.0 mm. The outer margin of each apron was marked by a sharply defined, hair-like line. Microscopically all of these outgrowths consisted of atypical flattened cells two to four layers deep with some bunching into a nodule at the outer margin. This outer margin seemed to advance between Descemet's and the endothelium, lifting up the latter, (fig. 9).

The sinus transplants, in the three in which both survived, formed small inactive cysts, lined by ciliated epithelium in two. In one of these (Experiment 48) the conjunctival graft had formed a rather large cyst that extended into the angle and invaded the root of the iris. This eye had suffered an iris prolapse and was probably glaucomatous. There was no connection between the epithelium on the surface and the cyst. In the third eye, in which both transplants survived, both formed large cysts that grew for a time and then receded. The larger one (table 4), (greenish in color)developed from the conjunctiva, although only a small portion of the lining looked like conjunctival epithelium. Most was flattened almost like endothelium. At the end of the experiment, the cyst of the sinus transplant could not be seen grossly or with the slitlamp. It was found microscopically and consisted in a small, very much flattened cyst lined by endothelial-like cells. In both of these shrunken cysts the epithelium looked atrophic.

TABLE 4

RESPIRATORY EPITHELIUM TRANSPLANTED WITH CONJUNCTIVA INTO THE SAME ANTERIOR CHAMBER (STUDY V)

Experiment No.	Postoperative Time Lapse (da.)	Transplant Present	Findings	
			Gross or Slitlamp	Histologic
			DOGS	
44	7	Yes C*		Both transplants fused together. Sinus transplant devoid of epithelium. Serial sections. Other covered by squamous epithelium outside (fig. 10)
45	22	Yes C, S†		Both transplants present and fused. Chief mass composed of dense connective tissue covered on outside with squamous epithelium and suspended between lens capsule and corneal incision. Different connective tissue on one side contains small cysts lined by respiratory epithelium. This part adherent to iris. Squamous epithelium does not extend out over the two suspending pedicles. Confined to transplant
46	79	Yes S	Transplant lies at pupillary margin on lens capsule	Sinus epithelium present on loose connective tissue. Open cyst is continuous with indeterminant epithelium on dense connective tissue. This looks like squamous epithelium but could be modified respiratory. No other squamous epithelium
47	98	Yes S	Iris adhesion to incision; small nodule of transplant incorporated in this	Multilocular cysts lined by ciliated epithelium. No squamous epithelium
			CATS	
48	32	Yes S, C	Iris prolapse Iris bombé.	Both transplants present: (1) simple cyst lined by ciliated epithelium. (2) conjunctival transplant consists of fibrous mass containing multilocular cysts lined by mucus-producing squamous epithelium. Exterior of mass covered by same and connects through surface openings with some of cysts. From main mass there is flat squamous outgrowth on posterior corneal surface and anterior iris. Extends to root of iris (See text)
49	37	No	Both transplants gone	
50	94	Yes C, S	White oval at corneal incision 1 by 2 mm. Apron-like outgrowth 1.5 mm.	Both transplants present. Respiratory inverted to make cyst. Conjunctival with epithelium on outside and extension of flat atypical out upon Descement's. Ends in nodule
51	94	No	Pigmented scar on cornea. Second pigmented scar on anterior lens capsule. Neither transplant recognizable	Pigmented small masses of fibrous tissue both on cornea and lens capsule. No epithelium found
52	156	Yes C	White nodule 1 by 2 mm. at corneal incision. Apron-like outgrowth 7 by 6 mm. on posterior corneal surface. Whole-mount showed this to be bleb	Transplant is from conjunctiva. Epithelium is outside and is modified and mucus-producing. Even found 3 ciliated cells. Outgrowth is composed of flattened cells. At the advancing margin the cells are bunched up to triple depth. Fibrin film (posterior wall of bleb) extends from margin back to transplant

* C = conjunctival epithelium.
† S = sinus mucoperiosteum.

TABLE 4 (*Continued*)

Experiment No.	Postoperative Time Lapse (da.)	Transplant Present	Findings	
			Gross or Slitlamp	Histologic
53	156	Yes C	White nodule 2.5 by 2.5 mm. surrounded by apron-like outgrowth 7 by 0 mm. Outgrowth area more clear than rest of eye	Nodule is conjunctiva with epithelium on outside. Flat atypical cells over Descemet's. End in nodule (cross section of ridge). Film of fibrin spans from this back to nodule (fig. 9)
54	393	Yes C, S	Nothing happened for 51 days. At 60 days 2 cysts present at incision—1 pink, 1 green. Both grew larger, until at 158 days—pink 2 by 3 mm., green 10 by 10 mm. At 200 days pink cyst gone. Pigment plaque marks spot. Green 7 by 12 mm. At 393 days, green cyst 7 by 5 mm. (fig. 13)	The larger, green, cyst is lined by conjunctival epithelium—part typical and part very much flattened. Sinus transplant represented by pigmented scar on posterior corneal surface containing tiny flat cyst lined by endothelial-like cells (fig. 13)

Discussion

In all, 65 epithelial transplants were made in these five studies.

Corneal epithelium survival

The first 20 transplants were from the cornea—eight by scraping and 12 by trephine buttons. The epithelium did not survive beyond 21 days in any. The scrapings left no trace after injection.

Frontal sinus vs. conjunctival epithelium survival and growth

Comparison was made between the survival and growth of frontal sinus epithelium versus conjunctival. Forty-five transplants were made—20 of frontal sinus mucoperiosteum and 25 of conjunctiva. The animals were permitted to live after operation from six hours to well over a year in some instances (tables 2, 3, and 4). Nine transplants of mucoperiosteum and 14 of conjunctiva were made alone into single eyes. In addition to these single transplants, both types of epithelium were transplanted into each of 11 eyes—22 transplants.

There was no significant difference between the two types of epithelium in the proportions that survived. Just over half of each managed to survive (sinus epithelium—11 of 20; conjunctival 13 of 25). Comparing the survival rate of those transplanted singly and in pairs there seemed to be no significant difference.

Adhesion formation between transplant and host

All of the transplants that survived became attached to the corneal incision or the iris or lens capsule, with the exception of those instances in which the animals were killed before there was time for adhesions to form. All that became attached seemed to establish a circulation either through the iris or the incision. In the latter instance, the cornea became vascularized between the incision and limbus.

One wonders at first how the adhesions between the transplant and host tissues are formed, especially adhesions to the incision when the transplant is deposited far away on the other side of the anterior chamber. The key to the process of attachment seems to be the coagulum of the secondary aqueous that forms within minutes after the operation. It takes several days for this coagulum to absorb, meanwhile fibroblasts grow out from the connective tissue of the transplants, as in tissue culture (Experiment 44, fig. 10).

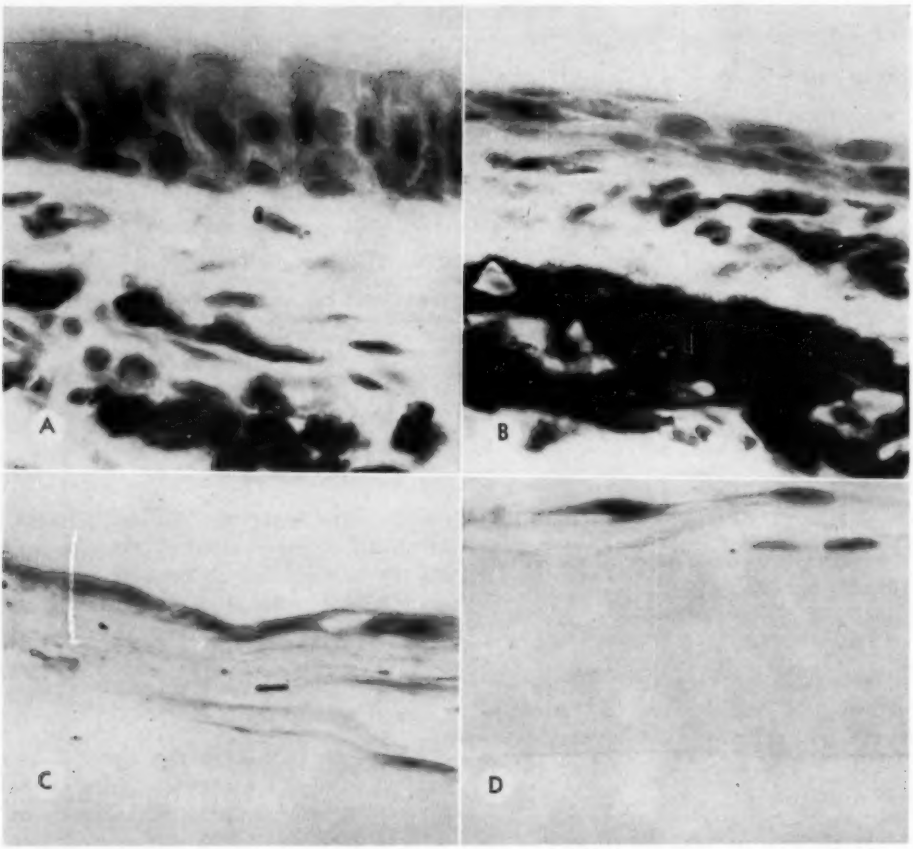

Fig. 8 (Hilding). Histologic findings in "healed" sinus transplant after 393 days in anterior chamber. The submucosa was completely covered by epithelium and had ceased to grow. The epithelium advanced upon the host tissue as far as it could, apparently, and then also ceased to grow. It ended in a feather-edge of modified, atrophic (?) cells. (A) Sinus epithelium growing upon its own lamina propria. (B) Sinus epithelium growing upon iris. (C) Sinus epithelium growing upon new fibrosis. (D) Sinus epithelium growing upon lens capsule.

They also grow out from divided corneal stroma at the incision. These fibroblasts partially organize the coagulum, thus forming fibrous pedicles and spanning synechias. Some adhere to the iris. It could not be determined if the adhesions to the iris occurred at traumatized spots or if the fibroblasts adhered to the iris stroma through intact endothelium.

Fate of transplants

The final condition of the transplants varied considerably. Some formed cysts that grew in size for a time and then receded; some remained for long periods neither growing nor receding, while others absorbed in a few weeks. Some of the conjunctival transplants formed so-called "epithelial pearls" and from some of these in turn an apronlike outgrowth or halo developed.

None of the eyes was destroyed or even seriously impaired by the transplants, with the exception of Experiment 36, the 131-day eye described in Study IV.

Epithelial pearls

Nine conjunctival transplants took the form of epithelial pearls—one or two mm. rounded white nodules (fig. 11). These pearls did not grow as in tissue culture. Growth seemed to cease when the lamina propria and submucosa became covered with epithelium. The epithelium feathered out at the margins in atrophic, flat cells and ceased to grow except in a few instances where a small outgrowth occurred upon host tissue (see below). Perhaps it can be said that the pearl has healed. Involved in the process are probably the organizational forces discussed by Friedenwald,[7] as well as nutritional factors.

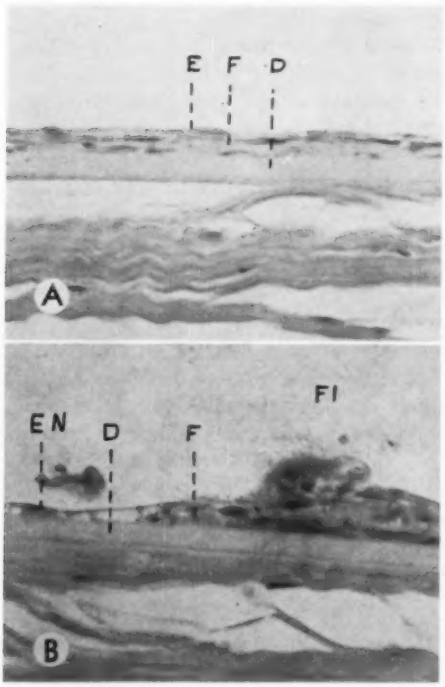

Fig. 9 (Hilding). (A) Flat squamous epithelium growing out onto cornea from conjunctival transplant: (E) epithelium, (F) fibrous layer, (D) Descemet's. (B) Advancing margin: (EN) normal endothelium, (D) Descemet's, (F) fibroblast insinuating itself under Descemet's, (FI) fibrin layer that spanned back to transplant.

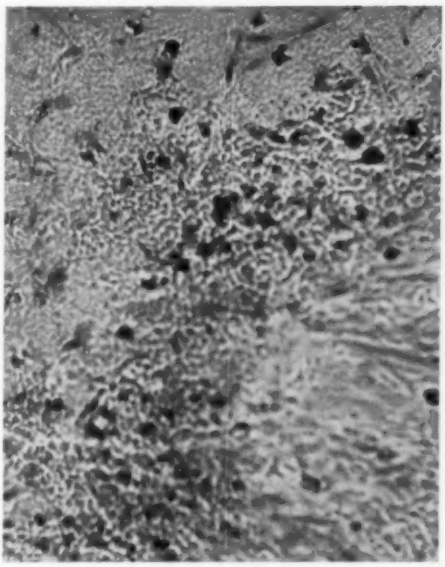

Fig. 10 (Hilding). Fibroblasts from the submucosa of the sinus transplant invading the aqueous coagulum after seven days.

Outgrowth of epithelium

Some degree of outgrowth of epithelium over host tissue occurred in eight experiments (table 5), six from conjunctiva and two from sinus mucosa. They varied in radius from microscopic dimensions up to seven

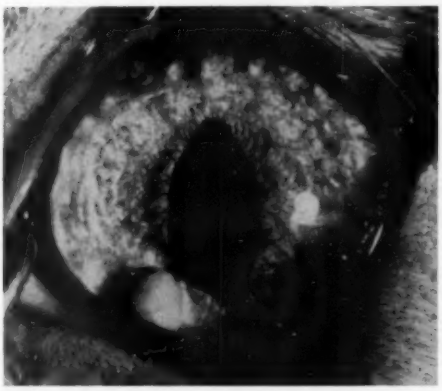

Fig. 11 (Hilding). Conjunctival transplant after 274 days in anterior chamber. It formed a "pearl" that remained unchanged for many months.

mm. The site of outgrowth was posterior corneal surface in five, iris two, and lens capsule one.

The two largest plaques (7.0 by 6.0 and 7.0 by 10) occurred in the two eyes of one animal killed 156 days after operation. None of the others exceeded two mm. in radius although the duration of two of these experiments was more than a year. The outgrowth did not occur equally on all sides of the transplants. When on the cornea, it was greater on the side toward the center.

The margin of these corneal outgrowths was very sharply defined by a tiny gray line. Microscopically, this line was found to consist of a tiny ridge of cells that, in cross section, appeared like a nodule, (fig. 9B). For some reason that is not clear, there extended from this ridge or line a friable, fibrinous membrane that spanned back to the transplant, enclosing a space to form a flat cyst. The anterior limit of this "cyst" was the curved cornea and the posterior the membrane in question. Histologically this membrane proved to be fibrinous and without cellular structure. A few neutrophils and other wandering cells were found in it.

The epithelial outgrowth on the cornea came from conjunctival transplants and consisted of a layer of modified squamous epithelium, two or three cells deep, lying upon a thin fibrous layer, which in turn lay upon Descemet's. The margin just described seemed to insinuate itself under the corneal endothelium and to lift the latter from Descemet's (fig. 9B).

Only one of the conjunctival transplants on the iris exhibited epithelial outgrowth. However, it did not prosper, even after 274 days it had advanced only 0.25 mm. on one side of the pedicle and 0.5 mm. on the other. It consisted in a single layer of cuboidal cells that ended abruptly in three or four irregular cells (fig. 5).

One of the outgrowths from sinus epithelium occurred on the anterior lens capsule. The duration of the experiment was 393 days and yet the extent of the outgrowth was only 0.75 mm. on one side and 1.75 on the other. It ended in a very flat type of endo-

TABLE 5

OUTGROWTHS (FROM STUDIES III, IV, AND V)

Experiment No.	Days	Tissue	Site	Width	Remarks
24	21	Conjunctiva	Cornea	Microscopic	Very tiny Questionable
28	274	Conjunctiva	Iris	0.25–0.50 mm.	
34	Living (1 yr.)	Conjunctiva	Cornea	1–2 mm.	Still living
42	393	Sinus	Lens capsule	0.75–1.75 mm.	Limited to capsule Does not go on iris
46	79	Sinus	New fibrosis on iris	0.5	Double sheet new endothelium extends into angle
50	94	Conjunctiva	Cornea	1.5 mm.	Halo
52	156	Conjunctiva	Cornea	7×6 mm.	On central side of graft
53	156	Conjunctiva	Cornea	7×10 mm.	On central side of graft
8		Conjunctiva..6 Sinus.....2	Cornea.....5 Iris.....1 New fibrosis..1 Lens capsule..1	—2	

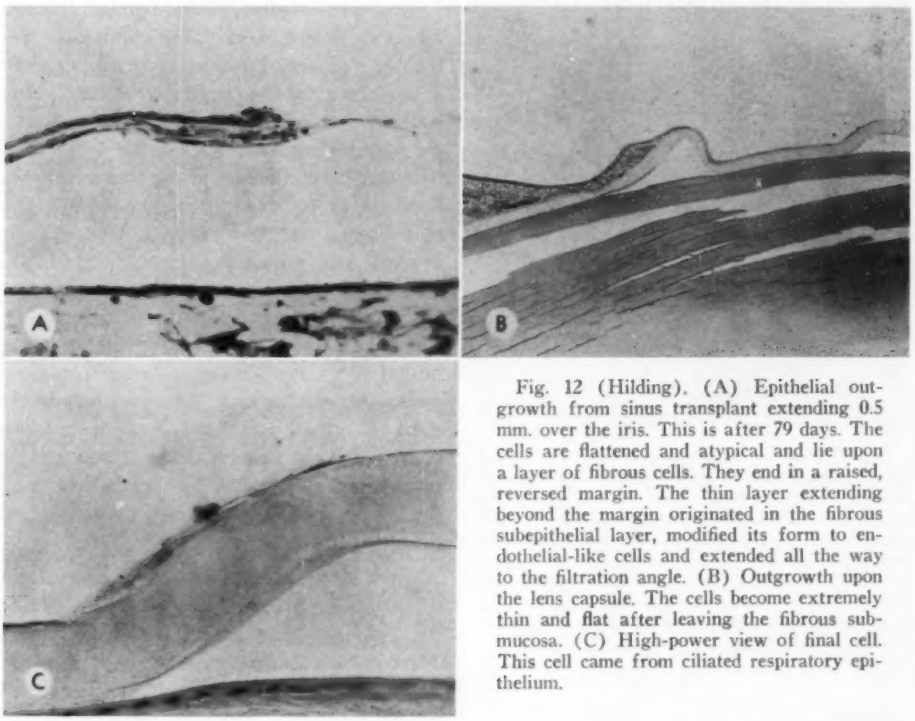

Fig. 12 (Hilding). (A) Epithelial outgrowth from sinus transplant extending 0.5 mm. over the iris. This is after 79 days. The cells are flattened and atypical and lie upon a layer of fibrous cells. They end in a raised, reversed margin. The thin layer extending beyond the margin originated in the fibrous subepithelial layer, modified its form to endothelial-like cells and extended all the way to the filtration angle. (B) Outgrowth upon the lens capsule. The cells become extremely thin and flat after leaving the fibrous submucosa. (C) High-power view of final cell. This cell came from ciliated respiratory epithelium.

thelial cell, much like the endothelium in the alveolus of the lung. In fact, this transplant showed progressive metaplasia reminiscent of the different types of respiratory epithelium from that of a sinus to that of the alveolus in a space of less than one mm. as the epithelium left its own lamina propria and extended out onto the lens capsule. This gradation could have been a phenomenon of insufficient nutrition[8] from the base upon which the epithelium lay (fig. 8).

The other sinus outgrowth presented an odd, complicated situation, described in figure 12.

Cysts

Many of the transplants that became inverted formed tiny cysts, some of them microscopic in size. Most of these did not grow appreciably larger. Five did grow considerably larger, only to recede as time went on. (For example, one reached a maximum of 8.0 by 10 mm. at 50 days and receded to 3.0 by 4.0 mm. at 126 days; another reached a maximum of 8.0 by 10 mm. at 20 days and receded to 3.0 by 6.0 mm. at 30 days; another, Experiment 54, is detailed in table 4, fig. 13.) None grew so large as to destroy the eye from pressure.

Summary and Conclusions

Sixty-five transplants of corneal, conjunctival, and sinus tissue were made into the anterior chamber. Eight of the corneal were scrapings of epithelium and 12 were trephine buttons. The epithelium did not survive in any beyond 21 days.

The survival and growth of conjunctival epithelium was compared with sinus epithelium. There was no significant difference. If a specific antibody directed against conjunctival epithelium exists, this study gave no

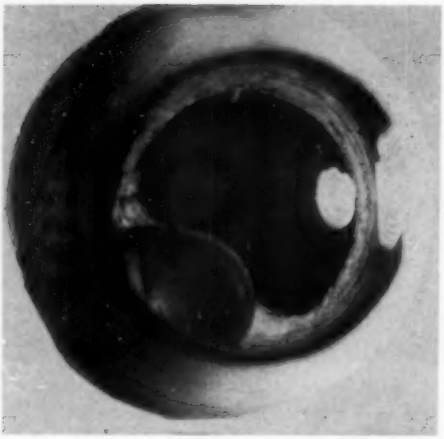

Fig. 13 (Hilding). Epithelial-lined cyst from conjunctival transplant. This cyst grew larger for six months and then receded (see text). Sinus mucoperiosteum was also transplanted into this eye. This grew larger for four months and then receded and finally disappeared grossly, leaving the leukoma seen in the upper half of the pupil. Microscopically the leukoma proved to be a pigmented fibrous layer lying upon the posterior corneal surface and containing a tiny, flattened cyst, lined by endothelial-like cells.

indication of it.

Approximately half of the conjunctival and sinus transplants survived until death of the animal. Some for more than a year. All of these had established a blood circulation either from the iris or the cornea at the incision.

Most of the surviving transplants did not increase in size as in tissue culture but remained unchanged for long periods of time as illustrated by the "epithelial pearls." This stationary condition apparently represents the status after healing.

When the epithelium of the transplant was inverted to form epithelial-lined cysts, the epithelium grew until it met itself. When everted and covering the outside of the transplant, this did not happen. In most, it feathered out to a flat, atrophic margin; in a few it advanced a few millimeters upon the host tissue. Cysts that grew larger for some weeks or months and then receded developed from five transplants. Some were from conjunctiva and some from sinus mucoperiosteum. In three of these epithelium lined the cyst, and in two it covered the outside of the cystic mass.

St. Luke's Hospital (11).

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REFERENCES

1. Hilding, A. C.: Corneal epithelium and penetrating corneal defects in cats: with special reference to epithelial downgrowth. Am. J. Ophth., **48**:787 (Dec.) 1959.

2. Dunnington, J. H.: Ocular wound healing with particular reference to the cataract incision. Arch. Ophth., **56**:639-659 (Nov.) 1956.

3. Theobald, G. D., and Haas, J. S.: Epithelial invasion of the anterior chamber following cataract extraction. Tr. Am. Acad. Ophth., May-June, 1948, pp. 470-485.

4. Cogan, D. G.: Experimental implants of conjunctiva into the anterior chamber. Am. J. Ophth., **39**: 165-172 (Apr. Pt. II) 1955.

5. Goldzieher, W.: Ueber Implantationen in die Vordere Augenkammer. Arch. f. exper. Path. & Pharmakol., **2**:387-404, 1874. (Cited by Theobald, G. D. and Haas, J. S.: Epithelial invasion of the anterior chamber following cataract extraction. Tr. Am. Acad. Ophth., May-June, 1948, pp. 470-485.

6. Kornbleuth, W., and Tenebaum, E.: The inhibitory effect of aqueous humor on the growth of cells in tissue cultures. Am. J. Ophth., **42**:70-74 (July) 1956.

7. Friedenwald, Jonas S.: Recent studies on corneal metabolism and growth. Cancer Research, **10**:461-466 (Aug.) 1950.

8. Fell, H. B., and Mellanby, E.: Metaplasia produced in cultures of chick ectoderm by high vitamin A. J. Physiol., **119**:470-488 (Mar.) 1953.

THE EFFECT OF CARBONIC ANHYDRASE INHIBITION ON INTRAOCULAR PRESSURE OF RABBITS WITH DIFFERENT BLOOD CO_2 EQUILIBRIA*

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Carbonic anhydrase is presumably necessary for the maximal secretion of aqueous humor. Under normal conditions inhibition of the enzyme reduces the aqueous flow and thus the outflow pressure by approximately 50 percent (Becker[1]).

Friedenwald[2,3] predicted on theoretical grounds that under changed acid-base conditions the ocular response to carbonic anhydrase inhibition should be altered. This is the case for another carbonic anhydrase dependent organ, that is, the kidney; Maren[4] found that either base loss or acid gain (metabolic acidosis) diminishes or even abolishes the renal effect of the carbonic anhydrase inhibitor acetazolamide. Carter et al.,[5] reported that in chronic respiratory acidosis, acetazolamide elicited no cumulative alteration in excretion of NH_4^+ and titratable acid, suggesting absence of renal effect. Brodsky, et al.,[6] found that in acute respiratory acidosis the typical renal action of acetazolamide in eliciting bicarbonate excretion, was markedly diminished.

Little information is available on the effect of changed acid-base balance on the eye pressure response to carbonic anhydrase inhibition. Becker[1,7] found that metabolic acidosis either enhanced or did not change the effect of acetazolamide on the eyes of rabbits, dogs or man, whereas Campbell, et al.,[8] reported that in man following pretreatment with oral ammonium chloride the expected fall in eye pressure following acetazolamide did not occur.

The present investigation has been undertaken as a further study of this problem.

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MATERIAL AND METHODS

ANIMALS

Male and female albino rabbits were used. They were kept for at least one week before the experiments, and were maintained on Purina Rabbit Chow,® carrots and tap water ad lib. The experiments were done from January to July.

MEASUREMENT OF INTRAOCULAR PRESSURE

Intraocular pressure was measured by means of tonometry according to a previously described technique and using a standardized Schiøtz tonometer (Riester) with the 5.5 gm. weight.[9] The standard error of the measurement of the pressure of one eye was ± 0.35 scale division (three readings). A calibration curve[5] from the eyes of living rabbits eyes was used.

The effect on the eye pressure was expressed as percent change of the outflow pressure. This makes it possible to compare effects in animals with different initial intraocular pressures. The outflow pressure has been defined[10] as the measured intraocular pressure minus the episcleral venous pressure, the latter pressure was taken to be 9.0 mm. Hg.[11] The episcleral venous pressure has been found to be unaffected by a number of factors such as carbonic anhydrase inhibition,[12] cervical sympathetic ganglionectomy,[13] ligation of the common carotid artery[11] or general anesthesia[14] and it was assumed to be constant (see, however, report of Macri[15]) also during the present experiments. The effect on the outflow pressure was calculated for each individual animal and these data were added within each group of rabbits and treated statistically. Student's t-test was used to compute the

significance of the differences between the groups.

Determination of CO_2 equilibria of blood

Blood was taken anaerobically (under mineral oil into stoppered tubes) from the median ear artery or from the heart. Its pH was determined within five minutes at 38°C. (Cambridge pH-meter model R, glass electrode SK-8625, Beckman buffer no. 3581). The plasma was separated within ten minutes by centrifugation at 22°C. and its content of total CO_2 was determined using a micro van Slyke method (Kopp-Natelson, Microgasometer, model 600).

Methods for changing blood CO_2 equilibria of rabbits

In the control series of rabbits, handled in the same way as in the present experiments, the plasma total CO_2 and pH were found to average 22.0 mM/l and 7.42 (fig. 1). An animal was considered in metabolic alkalosis when total CO_2 was 26.5 mM/l ($+2\sigma$) or more, and in metabolic acidosis when total CO_2 was 17.5 mM/l (-2σ) or less.

Metabolic alkalosis was induced by giving sodium citrate orally or by infusing sodium bicarbonate intravenously.

Citrate was given in a dose of 10 mM/kg body weight as a 10-percent solution of the sodium dihydrate ($C_6H_5Na_3 + 2H_2O$) through a stomach tube. In a pilot experiment we tested whether this way of administering citrate affected the eye pressure. In four rabbits the pressures of both eyes averaged 17.6, 22.7, 22.3 and 19.7 mm. Hg and at three hours following the administration of sodium citrate the pressures of the same eyes were 19.9, 22.7, 22.1 and 18.3 mm. Hg, respectively. These rabbits were alkalotic; total CO_2 in plasma was 29.3 mM/l and blood pH was 7.70 (mean values). Evidently the eye pressures were not significantly affected by the alkalosis. The effects of acetazolamide were tested five hours after the citrate administration. Preliminary experiments had shown that if this time was

1	2	3	4	5	6	7	8	9	10	11	12
EXPERIMENTAL GROUP	NO. OF RABBITS	WEIGHT KG	TWO MINUTES BEFORE ACETAZOLAMIDE		INTRAOCULAR PRESSURE, mm Hg			REDUCTION IN OUTFLOW PRESSURE, %			ACETAZOLAMIDE IN PLASMA, μg/ml
			Plasma total CO_2, mM/L	Blood pH	Initial	In acidosis or alkalosis prior to drug	30 minutes after drug	In acidosis or alkalosis (from col. 6 to 7)	After drug (from col. 7 to 8)	Total effect of acid base change plus drug (from col. 6 to 8)	35 min. after inj.
NORMAL	10	2.7	22.0 ±0.9 (8)	7.42 ±0.009 (8)	21.8 ±0.35	—	17.4	—	35.0 ±1.3	—	44.6 ±6.8 (10)
ALKALOTIC 10 mM/Kg sodium citrate orally 5 hours before drug	12	2.5	32.3 ±0.8 (12)	7.54 ±0.027 (9)	20.6 *	19.7	18.7	+3.0 *	8.1 ±6.8		68.0 (2)
ALKALOTIC 14 mM/Kg $NaHCO_3$ infused for 90 minutes before and 30 min. after drug	11	3.3	30.1 ±0.6 (11)	7.66 ±0.035 (5)	20.4 ±0.65	19.3	18.1	8.6 ±10.3	3.0 ±13.6	19.1 ±7.0	48.2 ±7.2 (11)
ACIDOTIC 15 mM/Kg NaCl infused for 90 minutes before and 30 min. after drug	7	2.9	14.4 ±1.3 (7)	7.30 ±0.030 (5)	22.4 ±0.71	17.7	15.4	31.9 ±4.4	16.2 ±4.3	42.0 ±5.8	25.0 (4)
ACIDOTIC Inhalation of 5% CO_2 for 120 min. before and 30 min. after drug	12	2.7	30.8 † ±1.9 (8)	7.28 † ±0.012 (8)	21.6 ±0.50	19.8	17.7	17.7 ±3.4	18.0 ±3.3	31.0 ±5.4	

Fig. 1 (Wistrand and Maren). The effect of acetazolamide (40 mg./kg. i.v.) on the outflow pressure (measured intraocular pressure minus episcleral venous pressure) of albino rabbits with different blood CO_2 equilibria. Data given are average values ± s.e.m. Figures within brackets indicate number of rabbits. * These sets of data were compiled in a separate group of four rabbits, given the same dose of sodium citrate (see methods). The plus indicates an increase of the outflow pressure. † Separate group handled in the same way as the eye pressure group.

extended to 24 hours, side-reactions (general weakness, diarrhea probably attributable to citrate intoxication[16]), usually developed at the same time as the alkalosis diminished. At five hours, however, the animals behaved normally and had plasma values of total CO_2 above 26.5 mM/l.

Sodium bicarbonate (0.47 M solution) was continuously infused by a pump via a long thin polyethylene tubing inserted into the marginal ear vein. The rabbit was wrapped in a cloth bag. During a period of 120 minutes, an average of 14 mM/kg. body weight of $NaHCO_3$ was infused. It was found difficult to establish a consistent high plasma level of bicarbonate in these infusion experiments (Green,[17] et al.) without the rabbit showing side reactions. An increase of the infused dose from 8.0 to 16 mM/kg. of $NaHCO_3$ raised the plasma level of total CO_2 from an average of 27 up to 31 mM/l. At this higher level, side-reactions started to develop in some rabbits which showed depressed activity, convulsions and finally paralysis of the hind legs. Later they also developed diarrhea and four out of 18 rabbits died within three to 34 hours after the start of the infusion. In three rabbits, however, the infusion only gave a slight increase of the plasma bicarbonate and they were not included in the experimental series.

Metabolic acidosis was induced by the intravenous infusion of a 0.47 M NaCl solution for 120 minutes. An average of 15 mM/kg. body weight were given. The effect of rapid intravenous NaCl infusion on the acid base balance has earlier been described (Shires and Holman[18]), and Van Slyke[19] called this effect "dilution acidosis." The technique of infusion was the same as described for the alkalotic rabbits. These rabbits did not develop any side reactions.

Respiratory acidosis was induced by keeping the rabbits in a gas chamber through which flowed a five-percent CO_2, 95-percent air mixture. The CO_2 content in the chamber was found to vary not more than ± 10 percent, during the experiment. Tonometry was performed on the rabbits in the gas chamber. The effect of the two hours exposure to this gas mixture on the acid-base balance was studied in a separate group of rabbits.

Carbonic anhydrase inhibition was induced by the intravenous injection of 40 mg./kg. acetazolamide (N.N.D.), a dose which 30 minutes after the administration to normal rabbits has been shown[9] to be maximally effective on the eye pressure.

Determination of acetazolamide in the plasma was done using the enzymatic method of Maren, et al.[20] The standard error of the method for measuring the concentration in one plasma sample was of an order of ± 7.0 percent (two determinations). Heparinized blood from the marginal ear vein was used.

Results

The results are shown in Figure 1. Rabbits made alkalotic by sodium citrate orally or sodium bicarbonate intravenously, had a normal or only slightly reduced intraocular pressure (fig. 1, cols. 7 and 9) as compared to normal rabbits or to the pressures before the induction of alkalosis (fig. 1, col. 6). Animals exposed to carbon dioxide and those infused with sodium chloride both showed significantly ($p < 0.01$) lowered eye pressures (fig. 1, cols. 7 and 9).

Acetazolamide had a variable effect on the eye pressures in the alkalotic rabbits, causing a large standard error. In the acidotic groups the inhibitor further reduced the already low pressures (fig. 1, cols. 7 to 8; col. 10).

The over-all effect of changed CO_2 equilibrium and acetazolamide is seen in figure 1, column 11. Reduction in outflow pressure was significantly less ($0.02 < p < 0.05$) in alkalotic rabbits than in the normal (fig. 1, col. 10). The greatest over-all effect was seen in the animals with metabolic acidosis; however when compared to the normal or to rabbits in respiratory acidosis, this increment was not significant ($0.1 < p < 0.02-0.3$).

In all experimental groups the plasma

concentration of acetazolamide 30 minutes after the injection (fig. 1, col. 12) was greater than the smallest concentration which maximally lowers the intraocular pressure. The plasma concentration necessary to evoke a maximal eye pressure response in normal rabbits has been found to be 10 to 20 μg./ml.[9]

Discussion

The effect of metabolic alkalosis and metabolic acidosis on intraocular pressure (fig. 1, cols. 7 and 9) agree with previously reported findings. Thus, Green, et al.,[17] saw no effect of metabolic alkalosis in rabbits infused i.v. with sodium bicarbonate isotonic plasma. During metabolic acidosis in rabbits or dogs, induced either by oral administration of ammonium chloride,[7, 21] or in rabbits by alloxan diabetes[22] the pressures were greatly lowered. No previous data seem to be available on the effect of respiratory acidosis on the eye pressure in rabbits. The low eye pressures both in respiratory acidosis and in metabolic acidosis, the latter condition being induced by different means, would suggest that it is the acideaemia rather than the CO_2 fractions (fig. 1, cols. 4 and 5) which is most closely related to the hypotonia. In what way acidosis affects the eye pressure remains to be established, although reports have appeared indicating a reduced aqueous humor flow[21, 22] and/or a reduced blood-aqueous barrier[21, 22] as possible reasons. In the discussion to follow the latter is neglected.

Changes in the osmotic activity of plasma relative to aqueous humor will transiently affect the eye pressure. But osmotic factors alone cannot be responsible for the low eye pressures observed in our rabbits infused with the hypertonic sodium chloride solution (fig. 1, cols. 7 and 9). This is evident from the difference in pressure between the rabbits infused with bicarbonate solution and with NaCl of the same molarity (fig. 1). No data are available on the acid base balance of the rabbits in previous experiments with hypertonic sodium chloride (Davson[23]) but it is possible that one additional factor causing the low pressures was a metabolic acidosis. Later in the discussion an attempt is made to explain how metabolic acidosis lowers the eye pressure by reducing the aqueous flow.

An attempt will be made to explain the differing sensitivity to acetazolamide during acidosis and alkalosis. The disposition of the drug is not much changed as is evident from the plasma concentrations (fig. 1, see col. 12). The properties of the inhibitor or the enzyme could be different which might interfere with the enzyme inhibitor interaction. However, it is known, from in vitro experiments, that the activity of the enzyme does not change[24] appreciably over a limited pH-range, such as that seen in our experimental animals. Since the first pKa of acetazolamide is 7.4 the fraction of ionized and unionized drug will be sensitive to physiological pH variations. An increase of 0.2 pH-units of the blood seen in the alkalotic rabbits (fig. 1) reduces the unionized fraction by about 30 percent. However, even if it were assumed that only the uncharged drug was pharmacologicially active, the effective plasma concentration in the alkalotic rabbits would still be on a maximally effective level.[9]

No data are available on the effect of pH on the interaction between acetazolamide and carbonic anhydrase.

The best explanation for the lowered intraocular pressure after systemic administration of carbonic anhydrase inhibitors is still, that these drugs act by inhibition of the enzyme in ciliary epithelium, thus reducing the aqueous humor secretion. Since the inhibitor also gradually alters acid base balance due to its red cell and kidney effect, it is reasonable to suppose that these secondary changes may also influence the eye pressure. No data[25] or reasoning[26] really contradict these assumptions; many experimental data support them.

The more intimate role of the enzyme for the aqueous secretion is, like in other secretory systems, a matter of speculation (Becker[1]). One theory is as follows: the

primary secreted rabbit aqueous humor is presumably alkaline. This can be explained by assuming hydrogen ions to be formed within the cell and transferred into the blood and possibly exchanged for some cation, probably sodium. Hydrogen is derived from metabolic water or from carbonic acid, the latter being formed by the catalyzed (carbonic anhydrase) hydration of carbon dioxide from the cell's own metabolism or from plasma. If water is the source of hydrogen the residual hydroxyl ions within the cell form bicarbonate by the catalyzed reaction with carbon dioxide. If carbonic acid is formed, bicarbonate enters the aqueous humor and hydrogen is carried into the blood, where it is ultimately buffered. In either situation the bicarbonate is transferred into the aqueous humor. It has been suggested that the aqueous flow is directly or indirectly related to this transfer.[2,3] In either situation carbonic anhydrase facilitates the bicarbonate transfer into the aqueous by catalyzing the hydration of carbon dioxide.

Changes of extracellular acid base balance are reflected, although, in a much damped fashion, within the cell.[27,28] During metabolic alkalosis the source of bicarbonate ions within the cell should be increased and the need for the enzyme for its formation should be less. The effect of an inhibitor should therefore be relatively small. The hydration of carbon dioxide occurs more rapidly, without catalyst in a more alkaline milieu. Conversely, during metabolic acidosis the source of bicarbonate ions would be small causing the secretion of aqueous to diminish and eventually the inhibition of the enzyme should further reduce the already low bicarbonate formation. In the case of respiratory acidosis the bicarbonate formation should reflect the net effect of the low cell pH impairing the bicarbonate formation and the increased carbon dioxide tension within the cell, tending to facilitate the formation of carbonic acid.

Provided the values of the eye pressures in the present experiments are directly related to the aqueous secretion, then these data (fig. 1) are consistent with the above hypothesis: namely that during aqueous secretion hydrogen ions are carried into the blood and bicarbonate into the aqueous humor. The kidney tubules supposedly exhibit an opposite situation. Here the directions of the bicarbonate and hydrogen transfers are reverse to those assumed for the rabbit eye; bicarbonate being carried into the blood and hydrogen into the urine.[31] In support of this analogy acidosis diminishes the renal response to carbonic anhydrase inhibition,[4,6] whereas it enhances the rabbit eye pressure drop.

It would be interesting to test in the same way eyes from species such as primates, in which the hydrogen and bicarbonate gradients between plasma and aqueous are opposite to those seen in rabbits.[29,30] Such differences in anterior or even posterior chamber data do not prove that the primary secretions are different in different species, but it has been suggested[1] that in the primate eye, hydrogen (and chloride) instead of bicarbonate (and sodium) is transferred into the aqueous humor and is related to the aqueous flow. However, if it were found that eyes from different species responded in the same way to various acid-base conditions and carbonic anhydrase inhibition, it would support the idea that the primary process of secretion across the ciliary epithelium is common to all eyes.

If the primary process of secretion in the human eye is similar to that in the rabbit, then it is clear why patients during long-term treatment of chronic glaucoma with carbonic anhydrase inhibitors do not become resistant to these drugs, although they sustain a metabolic acidosis.[32,33] It is evident that the systemic acidosis might add to the local effect of carbonic anhydrase inhibition.

Summary

1. Metabolic and respiratory acidosis lowered the intraocular pressure of albino rabbits.

2. Metabolic alkalosis did not affect the intraocular pressure.

3. The reduction in intraocular pressure due to carbonic anhydrase inhibition (injection of acetazolamide) was additive to prior reduction by metabolic or respiratory acidosis.

4. The normal effect of acetazolamide in reducing intraocular pressure was diminished by prior induction of metabolic alkalosis.

5. These data are consistent with the hypothesis that there is a bicarbonate (or hydroxyl) accumulating system in the formation of rabbit aqueous humor, partially dependent on carbonic anhydrase.

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REFERENCES

1. Becker, B.: Carbonic anhydrase and the formation of aqueous humor: The Friedenwald Memorial Lecture. Am. J. Ophth., **47**:342 (Jan. Pt. II) 1959.

2. Friedenwald, J. S.: Carbonic anhydrase inhibition and aqueous flow. Am. J. Ophth., **39**:59 (Feb. Pt. II) 1955.

3. ———: Current studies on acetazolamide (Diamox) and aqueous humor flow. Am. J. Ophth., **40**: 139 (Nov. Pt. II) 1955.

4. Maren, T. H.: Carbonic anhydrase inhibition: IV. The effects of metabolic acidosis on the response to Diamox® Bull. Johns Hopkins Hosp., **98**:159, 1956.

5. Carter, N. W., Seldin, D. W., and Teng, H. C.: Effect of Diamox on plasma and urine acid-base composition during chronic respiratory acidosis. Am. J. Physiol., **196**:919, 1959.

6. Brodsky, W. A., and Satran, R.: Comparison of effects of acidosis and alkalosis on the renal action of Diamox. Am. J. Physiol., **197**:585, 1959.

7. Becker, B.: The mechanism of the fall in intraocular pressure induced by the carbonic anhydrase inhibitor, Diamox. Am. J. Ophth., **39**:177 (Feb. Pt. II) 1955.

8. Campbell, D. A., Renner, N. E. A., and Tonks, E.: Effect of Diamox on plasma bicarbonate and on the electrolyte balance in relation to intraocular pressure in man. Brit. J. Ophth., **42**:732, 1958.

9. Wistrand, P.: The effect of carbonic anhydrase on intraocular pressure with observations on the pharmacology of acetazolamide in the rabbit. Acta Pharmacol. & Toxicol., **16**:171, 1959.

10. Goldman, H.: Studien über den Abflussdruck des Kammerwassers beim Menschen Ophthalmologica, **114**:81, 1947.

11. Kornblueth, W. D., and Linnér, E.: Experimental tonography in rabbits: Effect of unilateral ligation of common carotid artery on aqueous humor dynamics as studied by means of tonography and fluorescein in appearance time. A.M.A. Arch. Ophth., **54**:717, 1955.

12. Linnér, E.: Further studies of the episcleral venous pressure in glaucoma. Am. J. Ophth., **41**:646, 1956.

13. Linnér, E., and Prijot, E.: Cervical sympathetic ganglionectomy and aqueous flow. A.M.A. Arch. Ophth., **54**:831, 1955.

14. Stone, H. H., and Prijot, E.: The effect of a barbiturate and paraldehyde on aqueous humor dynamics in rabbits. A.M.A. Arch. Ophth., **54**:834, 1955.

15. Macri, F. J.: Acetazolamide and the venous pressure of the cat eye. Pharmacologist, **1**:56, 1959.

16. Ludbrook, J.: Citrate intoxication: A clinical and experimental study. Brit. Med. J., **2**:523, 1958.

17. Green, H., Mann, M. J., and Waters, L. P.: Elaboration of bicarbonate ion in intraocular fluids. I. Aqueous humors following intravenous infusion of sodium bicarbonate. A.M.A. Arch. Ophth., **57**:76, 1957.

18. Shires, G. T., and Holman, T.: Dilution acidosis. Ann. Intern. Med., **28**:557, 1948.

19. Peters, J., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Interpretations Volume 1. Baltimore, Williams & Wilkins, 1946.

20. Maren, T. H., Ash, V. J., and Bailey, E. M., Jr.: Carbonic anhydrase inhibition. II. A method for determination of carbonic anhydrase inhibitors, particularly of Diamox®. Bull. Johns Hopkins Hosp., **95**:244, 1954.

21. Langham, M. E., and Lee, P. M.: Action of Diamox and ammonium chloride on formation of aqueous humor. Brit. J. Ophth., **41**:65, 1957.

22. Cristiansson, J.: Changes in mucopolysaccarides during alloxan diabetes in the rabbit: II. Studies of intraocular pressure. Acta Ophth., **36**:163, 1958.

23. Davson, H.: Physiology of the Ocular and Cerebrospinal Fluids. Boston, Little Brown, 1956, p. 336.

24. Roughton, F. J. W.: Some recent work on the chemistry of carbon dioxide transport by the blood. The Harvey Lect., **39**:96, 1943.

25. Green, H., and Sawyer, J. L.: Elaboration of bicarbonate ion in intraocular fluids: VII. Studies with $NaHC^{14}O_3$ on the effect of Diamox on rabbit Aqueous Humor. Am. J. Ophth., **48**:71 (July, Pt. II) 1959.

26. Duke-Elder, S.: The aetiology of simple glaucoma. (The Bowman Lecture.) Tr. Ophth. Soc. U. Kingdom, **77**:205, 1957.

27. Caldwell, P. C.: Intracellular pH. Internat. Rev. Cytol., **5**:229, 1956.

28. Pitts, R. F.: Mechanisms for stabilizing the alkaline reserves of the body. The Harvey Lect., **43**: 172, 1953.

29. Davson, H., and Luck, C. P.: A comparative study of the total carbon dioxide in the ocular fluids, cerebrospinal fluid and plasma of some mammalian species. J. Physiol., **132**:454, 1956.

30. Becker, B.: Chemical composition of human aqueous humor: Effects of acetazolamide. A.M.A. Arch. Ophth., **57**:793, 1957.

31. Pitts, R. F., and Alexander, R. S.: The nature of the renal tubular mechanism for acidifying the urine. Am. J. Physiol., **144**:239, 1945.

32. Kupfer, C., Lawrence, C., and E. Linnér: Long-term administration of Diamox. Am. J. Ophth., **40**:673, 1955.

33. Becker, B., and W. H. Middleton: Long-term acetazolamide (Diamox) administration in therapy of glaucoma. A.M.A. Arch. Ophth., **54**:187, 1955.

SURGICAL TREATMENT OF DIVERGENCE EXCESS*

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INTRODUCTION

Although there is general agreement as to the surgical procedure best used for the correction of divergence excess, a review of the results obtained at the Mayo Clinic for the five-year period 1953-1958 may be instructive. This report is concerned with 27 patients whose ocular imbalance was classified as of divergence-excess type in that the divergence was greater for distant vision than for near, while the near point of convergence and the prism vergences at near vision were within normal limits. The surgical procedure was bilateral recession of the lateral rectus muscles.

Each patient was examined preoperatively and postoperatively by the same physician and orthoptic technician, the examination consisting of the prism cover test, the Worth four-dot test, and tests on the major amblyoscope. The latter was used to verify the ocular deviation and to determine the quality of fusion.

Two patients received orthoptic training preoperatively and postoperatively. Such training was not feasible with the other patients, since they lived at too great a distance to return to the clinic at regular intervals. Each patient had at least two postoperative examinations, however; and the data in this report are those of the latest examination. The interval after operation ranged from six months to five years.

PREOPERATIVE DATA

Frequently the age of onset of divergent strabismus is difficult to determine, and parents tend to discover the divergent tendency later in a child's life than they notice a convergent tendency. In only 10 patients (37 percent) of this group was the age of onset stated to be one year or less, while for 20 patients (74 percent) this age was up to 11 years. None was subjected to operation when less than four years of age, but 18 (67 percent) were not yet 11 years of age.

Each patient was given a test under cycloplegia for refractive errors. Twenty-one patients (78 percent) were mildly hyperopic, 17 of these having a refractive error less than one diopter. Six patients (22 percent) were myopic, five of these having a refractive error greater than one diopter.

The near point of convergence was less than eight cm. in 24 cases (89 percent), and that in the remaining three was between

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eight and 13 cm. The Worth four-dot apparatus showed that five patients (19 percent) had fusion for distance (20 feet) and 22 (81 percent) did not, whereas 22 had fusion for near vision (14 inches) and five did not.

On the cover test for distant fixation, all the patients selected had exophoria greater than 20 prism diopters and 22 (81 percent) of them had exophoria greater than 30 prism diopters. Nineteen patients (70 percent) were found to have intermittent exotropia. Among these, the exotropia was 20 prism diopters in five, 21 to 30 diopters in 13, and greater than 30 diopters in one. Only three patients (11 percent) exhibited frank exotropia for distant fixation. It measured between 21 and 30 diopters in two of these and greater than 30 diopters in one.

The cover test for near fixation revealed that 24 patients (89 percent) had less than 20 prism diopters of exophoria (four of these being orthophoric), whereas two had exophoria of 21 to 30 diopters, and only one (Case 18) had exophoria of more than 30 diopters. For each patient the deviation at near was found to be less than that at distant vision.

The quality of fusion was determined on the major amblyoscope. When tested for simulated distant vision, 23 of the patients (85 percent) had second-degree fusion with small amplitudes and six (22 percent) had stereopsis. On the test at near vision all 27 patients showed at least second-degree fusion and 18 (67 percent) showed stereopsis.

Surgical procedure

The optimal time for surgical correction of divergence excess has been variously stated by different authors. Scobee[1] suggested that a deviation of 18 prism diopters or greater at either distant or near vision was a sufficient indication. Although the divergence found in the patients of this series was 20 prism diopters or more, that exact amount was not taken as the sole indication. Most ophthalmic surgeons would agree that the primary indication for surgery is the increased divergence at distant vision which taxes the existing fusional ability. The concern felt by parents who may have noted an increasing tendency for divergence is a second factor to be considered. Any myopia must be fully corrected before operation. Advantages may be gained by the use of orthoptics both before and after operation to improve prism vergences. However, it has been our experience that preoperative training in fusion has little effect on the amount of the deviation. Two patients of our series received intensive orthoptic training, and they demonstrated quicker and slightly better recovery of prism vergences after operation than did those who had not been given this training.

In each case the surgery consisted of bilateral recession of the lateral rectus muscles. The amount of recession of each lateral rectus was varied according to the age of the patient primarily, so that for young children this was six mm. on the muscles of both eyes, while for older children and adults it usually was about seven mm. The amount was smaller in young children because their eyes were smaller. All patients therefore received what, in our opinion, was maximal recession. A greater amount would have placed the new insertion posterior to the equator of the globe, and thus would have tended to decrease the effective lateral action of the muscle. Each muscle was freed of check ligaments and of the intermuscular membrane as far posteriorly as feasible, the muscle sheath being left intact. Accordingly, the lateral muscles of 23 patients (85 percent) were recessed bilaterally about 6 mm., and in four patients (15 percent) these muscles were recessed about seven mm.

Surgical results

This report is not a comparison of the results of different types of surgical procedures for the treatment of divergence excess, but is rather a presentation of specific results from one consistently applied procedure.

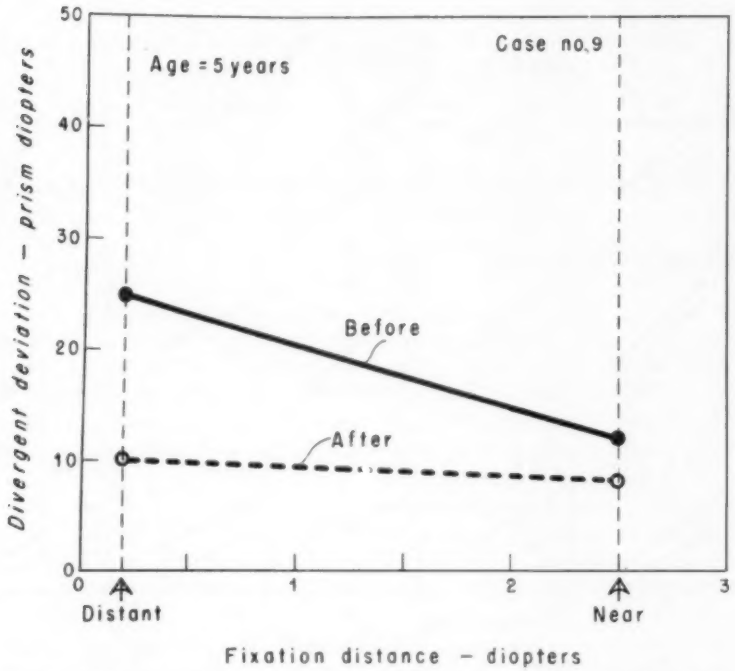

Fig. 1 (Dyer and Martens). Scheme for representing preoperative and postoperative divergence deviation at distant and at near vision. On the abscissa is the dioptric distance at which the tests were made: in distant vision, 5 meters equals 0.2 diopters; in near vision, 40 cm. equals 2.5 diopters. The ordinates are the measured ocular exophoric deviations in prism diopters. The filled circles indicate the ocular deviations prior to operation; the open circles indicate the deviations at the most recent testing after operation.

The ocular deviations before and after operation can be best visualized graphically. Figure 1 shows the method we have used for plotting, and Figure 2 indicates the changes effected in each of the 27 cases. A study of these figures shows the following:

1. In all cases the operation resulted in a reduction of the divergence for distant vision.

2. The deviation for near fixation was essentially unchanged by operation in 13 cases, having been about zero beforehand in most of them.

3. It was a clinical impression that large preoperative deviations for near vision were reduced, but small deviations of that sort were almost unchanged.

4. In six cases the reduction in the divergent deviation was about the same for both distant and near fixation distances.

5. In no case did the operation result in an overcorrection—that is esophoria.

The average distant deviation was 26 prism diopters (S.D. = 5.4 Δ) preoperatively and 13 (S.D. = 9.7 Δ) postoperatively, the average reduction being 12 (S.D. = 6.3 Δ). The average near deviation was 14 prism diopters (S.D. = 8.5 Δ) preoperatively and 7.5 (S.D. = 10.5 Δ) postoperatively, the average reduction being 5.2 (S.D. = 8.9 Δ). The standard deviation (S.D.) indicates that the results from about 68 percent of the patients were within plus-or-minus one standard deviation of the average.

Although the near point of convergence cannot be measured with precision, the results showed essentially no change in the

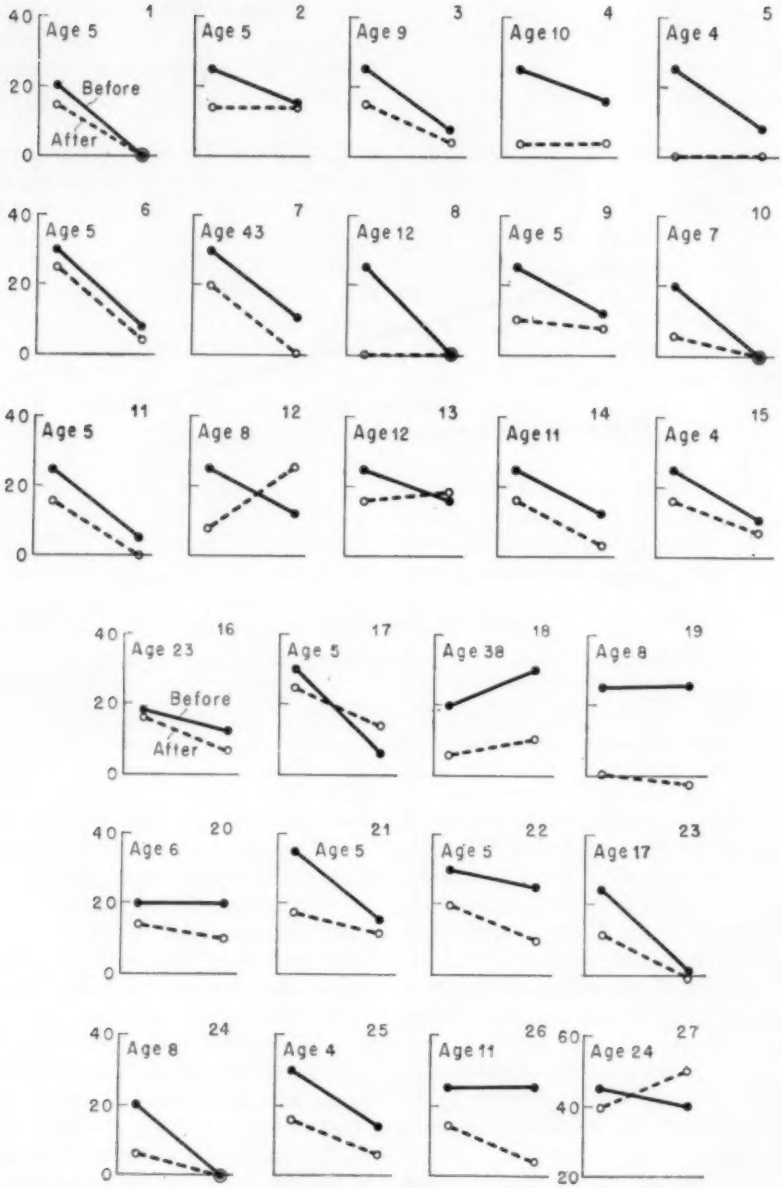

Fig. 2 (Dyer and Martens). Findings in 27 cases, presented by the scheme shown in Figure 1. Postoperative near findings as recorded in cases 12, 17, and 27 do not imply an increased divergence tendency, since the convergence and fusional amplitude were as good as preoperatively.

TABLE 1

QUALITY OF FUSION IN DISTANT VISION BEFORE AND AFTER OPERATION
(all 27 cases)

Evidence for Fusion	Second Degree		Stereopsis		Worth Four-Dot	
	No.	%	No.	%	No.	%
Preoperative	23	85	6	22	5	19
Postoperative	27	100	20	74	24	89

near point postoperatively.

In general, the quality of fusion measured postoperatively represented a very substantial improvement over the preoperative conditions (table 1). It was a clinical impression, also, that most of the patients had experienced more reduction in the divergent deviation as the time after operation lengthened.

COMMENT

Although this series of cases is a small one, it is reported to substantiate further the efficacy of bilateral recession of the lateral rectus muscles for patients with a divergence-excess type of ocular deviation. Certainly the onset of the deviation is variable, and the decision as to the optimal time for surgical intervention is still far from being definite. But it behooves the ophthalmic surgeon to operate before a recession of the near point of convergence and an increase in the exophoric deviation for near vision indicate a co-existing secondary convergence insufficiency that will require a more extensive surgical procedure. We give especially close attention to patients having a large exophoria for distant fixation, those having intermittent exotropia, and particularly those having a frank exotropia of 18 prism diopters or more with a normal convergence near point and little or no phoria at near fixation. If the exophoria for distant vision increases, or the near point of convergence recedes or near phoria increases, and if the child's parents note a more frequent divergence of the eyes, bilateral recession of the lateral rectus muscle is indicated.

Other authors have suggested modifications of this type of procedure. Sugar[2] noted that overcorrection in some cases resulted in postoperative esophoria, and accordingly he has urged that single or even bilateral small medial rectus recession be combined with the lateral rectus recessions. We have not found this secondary procedure necessary, since no overcorrection has occurred in our experience. If the lateral rectus recessions are not excessive, overcorrection is unlikely.

In his recent review of 54 operative cases of divergence excess, Johnson[3] found that a myopic refractive error greater than one diopter portended a poor result. Commonly it is noted that prescription of a necessary myopic correction improves existing exophoria. In our series, five patients had myopia greater than one diopter and three of these had myopia greater than four diopters. Each of these patients had excellent second-degree fusion and stereopsis following the surgical correction. It seems unlikely that myopia would be a serious deterring factor in surgical treatment of this type of ocular imbalance.

The results of the surgical procedure have implications important to the theoretical aspects of ocular motor imbalance. In only six cases of this series (6, 7, 11, 14, 15, and 19) did operation result in a parallel displacement of the ocular deviation, that is, an equal reduction of the exo-deviation at distant and near vision. A mechanical change in orientation of the eyes would be the only expected result of the operation; in the majority of cases the reduction in exo-deviation is not mechanical, for the deviation at near vision tends to approach orthophoria. On the basis of the mounting evidence[4] that

divergence is an active process, the symmetrical operative procedure used here could relieve the excessive muscular activity of the lateral muscles during distant vision but would have a much reduced effect when the eyes were fixated for near. So long as the ocular imbalance is a true divergence excess, identical surgical procedures on the two lateral muscles may be expected to yield satisfying results in the majority of patients.

Summary

A review of 27 cases of the divergence-excess type of deviation, each treated by recession of both lateral rectus muscles, has been presented in support of this surgical procedure. Operation had been advised for those patients with exophoria for distant vision of 18 prism diopters or more if the deviation was found to be increasing, or if the phoria for near vision was increasing and the near point of convergence receding and the parents had noted an increase in the frequency of divergence of the eyes. In all cases a bilateral recession of six to seven mm. was performed. The lesser degree was applied in the smaller patients; for those more than 14 or 15 years of age the greater amount was used. Overcorrection did not occur, so no supplementary procedure—concurrent or subsequent—has been necessary. The refractive error had little bearing on the surgical results in this series. Preoperative and postoperative orthoptic training may be used to advantage to improve fusional ability in some patients and to enhance the operative result, but it probably will not affect the amount of deviation. The results indicate that an improvement in quality of fusion occurred in the majority of the patients.

References

1. Scobee, R. G.: The Oculorotary Muscles. St. Louis, Mosby, 1952, ed. 2.
2. Sugar, Saul: The surgical treatment of divergence-excess: Types of intermittent exotropia. Am. J. Ophth., **42**:619-620 (Oct.) 1956.
3. Johnson, D. S.: Some observations on divergence excess. A.M.A. Arch. Ophth., **60**:7-11 (July) 1958.
4. Breinin, G. M.: The nature of vergence revealed by electromyography. A.M.A. Arch. Ophth., **54**: 407-409 (Sept.) 1955.

PERFUSION STUDIES ON EYES OF FOUR SPECIES*

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The well-known washing-out effect is generally recognized as representing the removal of some coating substance from the trabecular fibers of the filtration angle. Evidence obtained by several groups of workers fairly conclusively shows that hyaluronic acid is the substance which is removed when the anterior chamber of the eye is perfused with physiologic salt solutions.[1-4]

The work reported here represents an effort to gain some appreciation of how general the washing-out effect is among different animals. It was, therefore, thought to be of value to determine the time course and magnitude of the change in facility of outflow when enucleated eyes of four species of commonly used experimental animals were perfused with physiologic salt solution. It also seemed desirable to learn whether or not hyaluronidase affected the eyes of these different animals to the same extent.

Methods

Pairs of enucleated eyes from 10 cats, 12 dogs, 10 rabbits, and 10 guinea pigs were perfused simultaneously on identical appara-

* From the Department of Physiology, The University of Texas Southwestern Medical School. This work was supported by a research grant (B-999) from the National Institute of Neurological Diseases and Blindness, Public Health Service.

tus with Ringer-Locke solution (pH 7.4). The eyes were removed quickly from heparinized animals deeply anesthetized with sodium pentobarbital, cleaned of extraocular tissue, and mounted in beakers of Ringer-Locke solution which were suspended in a 37°C. constant temperature bath. No regard was given to which eye was removed first or which eye went on which apparatus. Generally, the second eye was removed 4-6 minutes after the first eye. Both the anterior chambers and vitreous compartments of all eyes were cannulated with 21-gauge needles which were connected by polyvinyl tubing and stopcocks to horizontal perfusion pipettes and reservoirs.

In all experiments perfusion was carried on continuously for 130 minutes. Determinations of facility were made every 10 minutes by measuring with a stopwatch the length of time necessary for 10 mm^3. to enter the eye. The perfusion pressure was 28.37 mm. Hg in all experiments. Facility, as used here, has the units of $mm.^3$ inflow per minute per mm. Hg. The details of the perfusion procedure have been previously described.[5]

The data from eyes on each perfusion apparatus were then averaged for each time interval and plotted. The mean values for corresponding times were analyzed by Student's t-test for significance of difference in the means.

One eye of each pair of eyes from 12 cats, 10 dogs, 10 guinea pigs, and 10 rabbits was perfused with Ringer-Locke solution as outlined above. This eye was designated as the control eye. One eye of each pair, designated as the experimental eye, was perfused with Ringer-Locke solution which contained 10 units of testicular hyaluronidase (Wydase) per cc. Liquification of the vitreous occurred in all of the experimental eyes. The concentration of hyaluronidase in the solution was, therefore, considered high enough to cause depolymerization of any trabecular hyaluronic acid within the time of the experiment.

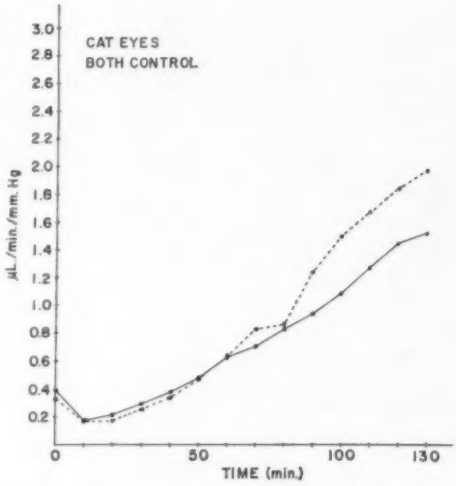

Fig. 1 (Melton and DeVille). Mean facility values of 10 pairs of cat eyes perfused with Ringer-Locke solution. None of the points corresponding in time are significantly different from each other.

Results

Cats

a. *Controls.* It was reported previously[5] that the enucleated cat eye had an initial facility of outflow of about 0.36. This value increased with time of perfusion to an average of 1.74 in 130 minutes (fig. 1). Comparison of the control curves in Figure 1 with the comparable control curve in Figure 2 shows the effect of changing operators on the data obtained. The data graphed in Figure 1 were collected by one operator while those in Figure 2 were collected by another. The reason for the difference in the two curves is intangible, but it is to be emphasized that the eyes must be handled very gently and the same operator must collect all data if consistent values are to be obtained. However, none of the mean values graphed in Figure 1 for corresponding times are statistically different from each other, nor are any of the points on curve 1 of Figure 2 different statistically from their corresponding points in Figure 1.

b. *Effect of hyaluronidase.* The data graphed in Figure 2 show that the eyes per-

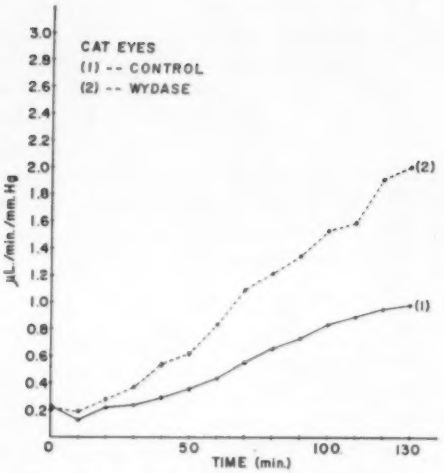

Fig. 2 (Melton and DeVille). Mean facility values of 12 pairs of cat eyes perfused with Ringer-Locke solution (Curve 1) and Ringer-Locke containing 10 units/cc. of testicular hyaluronidase (Curve 2). None of the pairs of points corresponding in time are significantly different.

fused with hyaluronidase had a higher mean facility of outflow at any given time than the control eyes. However, the elevation of the experimental curve is more apparent than real for it is not outside the deviation of the points on the control curve and none of the corresponding points on the two curves are statistically different. The control eyes had a mean initial facility of outflow of 0.23. This value increased in 130 minutes to 0.98. The average facility of the hyaluronidase-treated eyes was 0.22 initially and increased to 2.05 in 130 minutes.

While hyaluronidase in this concentration caused liquification of the vitreous body, it had a negligible effect in accelerating the washing-out effect.

Dogs

a. *Controls.* Initial facility values for 12 pairs of eyes perfused with Ringer-Locke solution averaged 0.21 for eyes run on one perfusion apparatus and 0.36 for those run on the other (fig. 3). These values increased after 130 minutes of perfusion to 0.94 and 1.01, respectively. The differences between points corresponding in time on the two curves were not statistically significant.

b. *Effect of hyaluronidase.* The dog experimental eye was similar to that of the cat in that the facility of outflow was elevated over the control eye (fig. 4). However, analysis of the differences between corresponding points on the two curves showed that the control and experimental values belonged to the same population. The control eyes averaged initially 0.25 and the experimental eyes averaged 0.26. These values increased in 130 minutes to 1.35 and 1.45, respectively. The effect of hyaluronidase could not, therefore, be distinguished from other factors contributing to differences between eyes on the two experimental arrangements.

Rabbits

a. *Controls.* The rabbit eye did not show the washing-out effect when perfused with Ringer-Locke solution (fig. 5). In fact, the means of the facility values after 130 minutes of perfusion (0.18 and 0.19) were slightly lower than the means of the initial

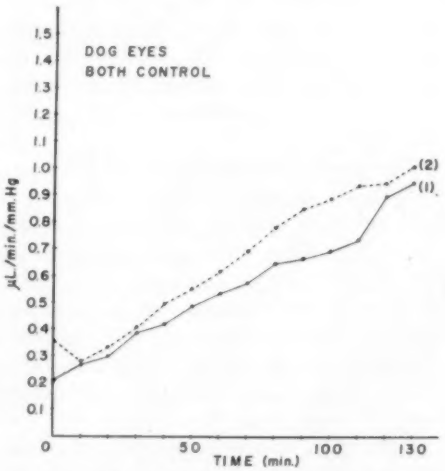

Fig. 3 (Melton and DeVille). Mean facility values of 12 pairs of dog eyes perfused with Ringer-Locke solution. None of the points corresponding in time are significantly different.

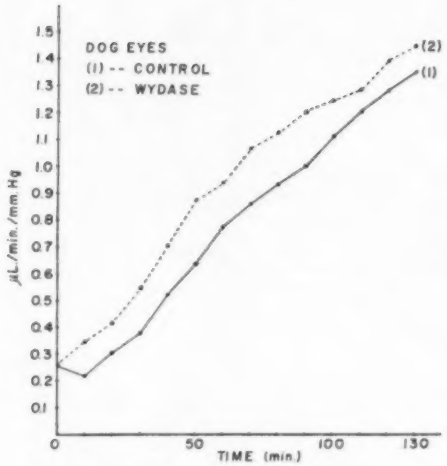

Fig. 4 (Melton and DeVille). Mean facility values of 10 pairs of dog eyes perfused with Ringer-Locke solution (Curve 1) and testicular hyaluronidase (10 units/cc.) in Ringer-Locke solution (Curve 2). None of the points corresponding in time are significantly different.

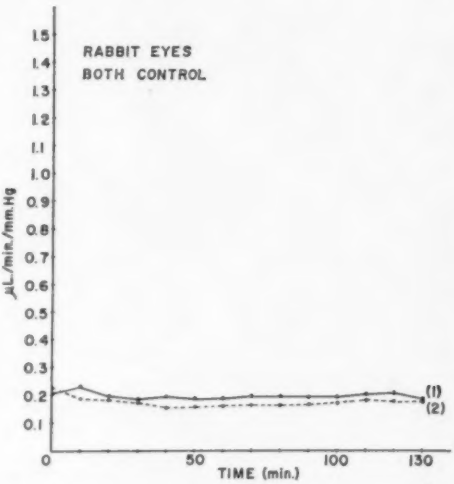

Fig. 5 (Melton and DeVille). Mean facility values of 10 pairs of rabbit eyes perfused with Ringer-Locke solution. None of the points are significantly different from each other.

values (0.20 and 0.23). Pairs of eyes from the same rabbits agreed closely with each other in their facilities of outflow as did eyes from different rabbits. The differences in corresponding points on the two curves of Figure 5 are insignificant.

b. *Effect of hyaluronidase.* The mean values of the hyaluronidase-treated eyes were significantly higher than the control values (fig. 6). The mean initial facility of outflow of the control eyes was 0.24 while that of the experimental eyes was 0.25. These values changed to 0.18 and 0.32, respectively, in 130 minutes. The experimental mean value was elevated over the control mean value by a doubtfully significant amount ($p < 0.05$) at the 40 minute determination. Thereafter, the differences in the means were highly significant ($p < 0.01$).

GUINEA PIGS

a. *Controls.* The guinea pig eye, like the

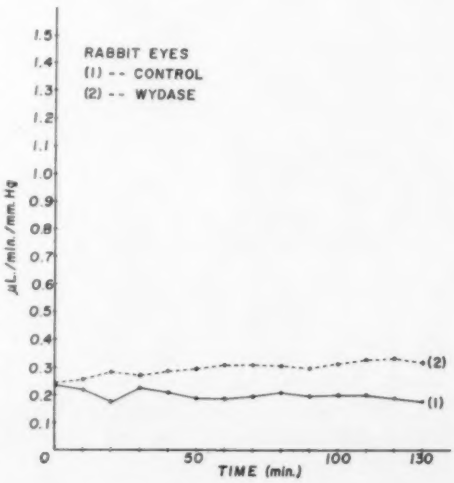

Fig. 6 (Melton and DeVille). Mean facility values of 10 pairs of rabbit eyes perfused with Ringer-Locke solution (Curve 1) and testicular hyaluronidase (10 units/cc.) in Ringer-Locke solution (Curve 2). Corresponding points from the zero time determination to the 40 minute determination are not significantly different. Control and experimental means at the 40 minute determination are different at the five-percent level of significance. The means are different at less than the one-percent level of significance from the 50 minute determination through the 130 minute determination.

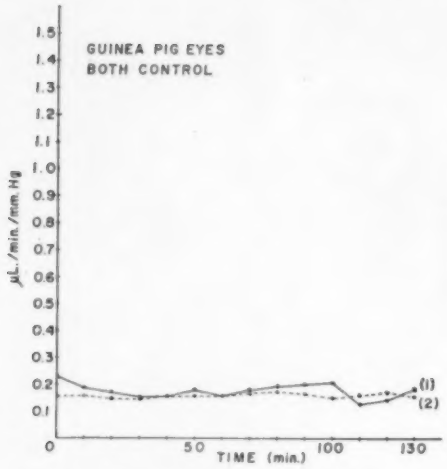

Fig. 7 (Melton and DeVille). Mean facility values of 10 pairs of guinea pig eyes perfused with Ringer-Locke solution. None of the points are significantly different from each other.

rabbit eye, did not show the washing-out effect (fig. 7). The mean of initial facility values obtained from eyes on one perfusion apparatus was 0.23 and from eyes on the other apparatus, 0.16. These values became 0.18 and 0.16, respectively, in 130 minutes. There was close agreement between the two sets of data, with none of the differences significant.

b. *Effect of hyaluronidase.* The enzyme-treated eyes showed a marked and immediate increase in facility of outflow (fig. 8). In fact, the effect was noticeable at the first determination when the difference between experimental and control eyes was of borderline significance ($p < 0.05$). The mean of the initial control values was 0.21; the mean terminal facility value of the controls was 0.23. The mean of the initial experimental values was 0.32; this value changed to 0.53 in 130 minutes. The differences between all corresponding experimental and control means were different at less than the one percent level of significance from the 10 minute determination through the 130 minute determination.

TABLE 1

THE WASHING-OUT EFFECT IN FOUR SPECIES

Animal	No. of Eyes	Average Initial Facility	Average Maximum Facility	Percent Change
Cat	20	0.34	2.30	576
Dog	24	0.28	1.02	264
Guinea pig	20	0.19	0.25	32
Rabbit	20	0.22	0.28	27

The values shown are the means of the highest facility values which occurred in each experiment and are not necessarily the means of the terminal values.

COMMENT

This investigation shows that of the four most commonly used experimental animals, rabbits and guinea pigs are the animals of choice for studies in which it is desirable to use one eye of a pair as a control and the other as an experimental eye. Members of pairs of rabbit and guinea pig eyes agreed closely in their facilities of outflow. Also,

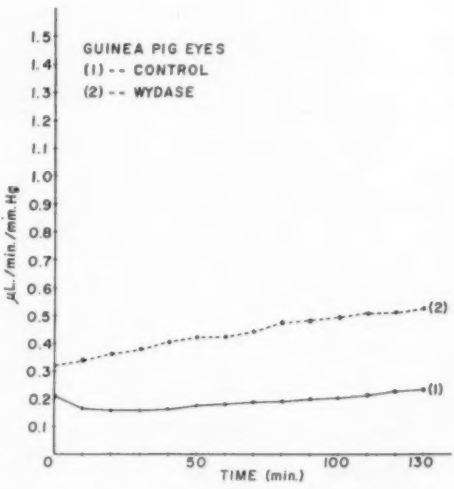

Fig. 8 (Melton and DeVille). Mean facility values of 10 pairs of guinea pig eyes perfused with Ringer-Locke solution (Curve 1) and testicular hyaluronidase (10 units/cc.) in Ringer-Locke solution (Curve 2). Points at zero time are different at the five-percent level of significance. All other points are significantly different at less than the one-percent level of significance.

TABLE 2

COMPARISON OF PERCENT DIFFERENCE IN FACILITIES OF FOUR SPECIES

			Cats		Dogs		Guinea Pigs		Rabbits	
			Initial	Maximum	Initial	Maximum	Initial	Maximum	Initial	Maximum
			0.34	2.30	0.28	1.02	0.19	0.25	0.22	0.28
Cats	Maximum	2.30								
	Initial	0.34		576						
Dogs	Maximum	1.02		125						
	Initial	0.28	21			264				
Guinea Pigs	Maximum	0.25		820		308	32			
	Initial	0.19	79		47					
Rabbits	Maximum	0.28		721		264		12	27	
	Initial	0.22	55		27		16			

pairs of eyes from different animals agreed closely.

Members of pairs of dog and cat eyes, on the other hand, often did not agree and neither did eyes from different dogs and cats. The reason for such lack of agreement may be related to anatomic differences between animals of various breed mixtures as well as to the comparatively poor general state of health and nutrition of cats and mongrel dogs obtained from the pound. Laboratory-reared rabbits and guinea pigs are such highly inbred animals that one specimen is pretty nearly identical in its physical attributes to any other of the same strain and age.

It has been reported that the facility of outflow is related directly to the volume of the anterior chamber.[6] This conclusion was based on plateau facility values after variable times of perfusion. Studies in this laboratory indicate that in the case of dogs and

cats the plateau facility value would be somewhat greater than the initial facility. In the case of guinea pigs and rabbits it would not be very different from the initial value.

Anterior chamber volumes were not measured in this study but it would be interesting to determine whether or not the constancy of the ratio of facility to volume of the anterior chamber holds up when the initial facility value is used instead of the plateau facility value. The initial facility values for all four species examined in this study are in closer agreement than are the maximum or terminal facility values (tables 1 and 2). Unless the facility of outflow of eyes of dogs and cats is initially depressed by the experimental procedure, the initial values prior to the washing-out of trabecular mucopolysaccharide, must be looked upon as the most "physiologic" of any of the determinations in these experiments. It seems, therefore, that the volume of the anterior chamber should be related to the initial value if conclusions are to be reached about the significance of the facility/volume ratio in vivo.

Comparisons of the initial and final or maximum facilities for all four species are summarized in Table 2. It is readily apparent from this chart that the great disparity in facility values for different animals lies in the maximum rather than in the initial facility of outflow. For example, the cat's maximum facility is 820 percent greater than the guinea pig's maximum; however, the cat's initial facility is only 79 percent greater.

If the washing-out effect is a measure of the removal of hyaluronic acid from the trabecular fibers, hyaluronidase should hasten the process. Such is the case with guinea pig and rabbit eyes. However, in cats and dogs the effect is negligible. The reason for this is not clear. It may be that the mucopolysaccharide in the filtration angles of these latter two species is so loosely bound that it is removed at a maximum rate by simple perfusion. It may also be that cat and dog eyes are more sensitive to trauma (massage effect of Bárány) associated with enucleation and cannulation than are guinea pig and rabbit eyes. This idea has not been tested.

Summary

1. Perfusion of enucleated eyes of dogs and cats with Ringer-Locke solution for 130 minutes caused a marked increase in facility of outflow. No such effect was demonstrated in the eyes of rabbits and guinea pigs.

2. Testicular hyaluronidase (10 units per cc.) had no discernible effect on the facility of outflow of cat and dog eyes but caused improvement in outflow from rabbit and guinea pig eyes.

3. The initial facility values of these four species were in closer agreement than were their terminal facilities.

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References

1. Bárány, E. H., and Scotchbrook, S.: Influence of testicular hyaluronidase on the resistance to flow through the angle of the anterior chamber. Acta Physiol. Scand., **30**:240, 1954.

2. Bárány, E. H., and Woodin, A.: Hyaluronidase and hyaluronic acid in the anterior chamber. Acta Physiol. Scand., **33**:257, 1955.

3. Zimmerman, L. E.: Demonstration of hyaluronidase-sensitive mucopolysaccharide in trabecula and iris in routine paraffin sections of adult human eyes. Am. J. Ophth., **44**:1, 1957.

4. Berggren, L., and Vrabec, F.: Demonstration of a coating substance in the trabecular meshwork of the eye and its decrease after perfusion experiments with different kinds of hyaluronidase. Am. J. Ophth., **44**:200, 1957.

5. Melton, C. E., and Hayes, D. W.: Modification of facility of outflow by perfusion of the vitreous chamber in the enucleated cat eye. Am. J. Ophth., **47**:657, 1959.

6. Becker, B., and Constant, M. A.: Species variation in facility of aqueous outflow. Am. J. Ophth., **42**:189 (Oct. Pt. II) 1956.

THE EFFECT OF CITRAL AND VITAMIN A*

On the intraocular dynamics of rabbits

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Introduction

Leach and Lloyd (1956) observed that citral was responsible for producing a rise in the intraocular pressure of monkeys and rabbits; this appeared an important clue toward solving the problem of the possible etiology of chronic simple glaucoma. Citral is an unsaturated aldehyde, and is found in nature in the peel of citrus fruits and in the oil of lemon-grass; hence it is likely to be present wherever the skin of citrus fruits is consumed by man, as for example, in marmalade, orange and lemon squashes, lime-pickles and so on.

In rabbits these workers claim that a single subcutaneous dose of 10 μg. of citral is enough to raise the intraocular pressure and that pressure instability results. They have further observed that the toxic effect of citral produced changes suggestive of a vitamin-A deficiency, and that the toxic action of citral could be prevented or reversed by vitamin A and sulfhydryl compounds such as cysteine and BAL. As citral is a highly toxic substance and if its toxic action is enhanced by vitamin-A deficiency as claimed, its consumption in the diet could be an important factor in ill health.

With regard to the mechanism producing raised ocular tension, Leach and Lloyd suggest that citral blocks the use of vitamin-A aldehyde in the endothelial cells of the trabeculae (where vitamin A has been identified). As the role of vitamin A in endothelial cells is probably one of taking part in an oxidation-reduction system, citral poisoning would cause a breakdown in endothelial metabolism. This means, they believe, a raised outflow resistance.

These observations of Leach and Lloyd appeared to us to be extremely important. Becker (1957) has mentioned them in his "Annual review of glaucoma," as did Moore (1957) in his book on vitamin A. Lennart Berggren (1957) has reported that citral did not raise the ocular tension in his series of rabbits, nor did it produce any alterations in the trabeculae.

In a series of about 350 preliminary observations in rabbits, we failed to obtain any rise in intraocular pressure with a single dose of citral as high as 26 mg. per rabbit. Similarly there was no significant alteration in the facility of outflow as found by tonography. Therefore, we wondered if perhaps a better technique might not be employed, especially as Eric Linnér (1958) has stated that tonometry and tonography alone may not always detect very early glaucomatous changes.

To cope with this Linnér devised a test, wherein variations in aqueous outflow resistance are produced by pilocarpine and Diamox (or similar substances), and the resultant ratios compared in healthy and diseased eyes. Since pilocarpine decreases the outflow resistance and Diamox increases it, what may be termed a "normal" range between them is obtained by tonography. This range is indicated by the ratio of the facility of outflow coefficient with pilocarpine (C_P) as compared to the facility of outflow coefficient with Diamox (C_D), the resistance to outflow being of course the inverse of facility of outflow ($C = \frac{I}{R}$). In patients with chronic simple glaucoma, Lin-

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nér found that the ratio $\frac{C_P}{C_D}$ was significantly altered, although straight tonography might not indicate any change. This test seemed to us to be just what we were looking for, affording, as it does, a uniformity of circumstance in each animal on every occasion of examination.

Methods

Group I. Rabbits on a vitamin-A deficient diet and given subcutaneous citral, 2.2 mg. per kg. body-weight, biweekly, over a period of six months. (Chronic citral poisoning.)

Group II. Rabbits on a vitamin-A deficient diet.

Group III. Control rabbits on stock diet.

Group IV. Rabbits on stock diet, given oral and subcutaneous citral, 26 mg. per day. (Acute citral poisoning.)

The techniques carried out were as follows:

1. Tonometry with the Schiøtz tonometer (5.5-gm. and 10.0-gm. weights), restrained and under Nembutal anesthesia.

2. Tonography with the Mueller electronic tonometer, obtaining tracings with the Sanborn recorder, restrained and under anesthesia (fig. 1).

3. The changeability test of Linnér was then applied to the rabbits of the four experimental groups, as follows: (a) initial tonography (C_I); (b) tonography after three-percent pilocarpine (C_P), thus: two instillations of pilocarpine at intervals of one hour (tonography was performed one hour after the second instillation); (c) tonography after Diamox (C_D), thus: Diamox (125 mg. per lb.) of body weight was given orally by stomach tube in two equally divided doses, at intervals of four hours (tonography was performed four hours after the second dose).

Fig. 1 (Rodger, et al.). Apparatus used. On the right a tonometer holder devised by us.

From the above data, the following three ratios were obtained:

$$\frac{C_P}{C_I}; \quad \frac{C_D}{C_I}; \quad \frac{C_P}{C_D}$$

Or simply, P/I, D/I, P/D

These ratios were analyzed comparing the behavior of the normal with the citralized rabbits. Citral was administered orally and subcutaneously, and both tonometry and tonography were carried out after 24 hours in all cases.

Repeated readings were taken, by tonometry and tonography, in the same animals at the same time of day to find out the experimental error of the animals.

On the whole, we preferred to carry out tonography under light Nembutal anesthesia, which kept the animal completely relaxed, so that the tracings were free from irregular fluctuations. Our preliminary observations showed that anesthesia did not significantly affect the results of tonography (fig. 2).

Results

1. Effect of citral on the intraocular pressure (tonometry)

Table 1 shows the means of the intraocular pressures (Schiøtz) in the four experimental groups of rabbits, along with the appropriate standard errors. It indicates that Group I (citral and vitamin-A deficiency) resembles Group III (control), and that the tensions in Group II (vitamin-A deficiency) and Group IV (acute citral) are slightly higher than in Groups I and III.

Table 2 shows the further decomposition

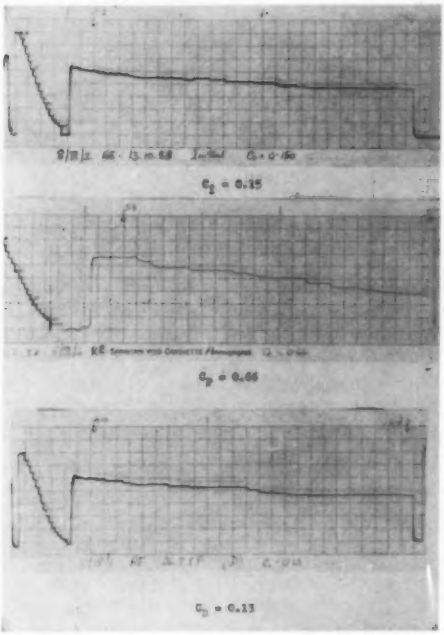

Fig. 2 (Rodger, et al.). Changeability tests in untreated rabbits.

of the "between groups means square" of Table 1 into three orthogonal components. The three linear components are $G_I - G_{III}$, $G_{II} - G_{IV}$, and $G_I + G_{III} - G_{II} - G_{IV}$. It can be seen from Table 2 that only the single degree of freedom corresponding to the last linear comparison is significant. Clinically this is a minor change. In other words, citral did not cause a significant rise in tension.

2. Effect of citral and vitamin-A deficiency on tonography

The four groups of rabbits were subjected to the changeability test, altering the facility of outflow with pilocarpine and Diamox. The readings thus obtained were converted into the three ratios P/I, D/I, and P/D respectively, as shown in Table 3. Then the analysis of variance was done for each of the ratios as given in Table 4, a, b, and c. Table 5 shows the mean values of the three ratios for the four experimental groups; there was no significant difference in the behavior of the four groups of rabbits in respect to the ratios P/I, D/I, P/D. Thus citral, with or without vitamin-A deficiency, did not alter the capacity to vary the outflow.

Discussion

We had hoped that by using oral and subcutaneous citral in rabbits we might have produced a significant rise in tension or alteration in the facility of outflow, as a preliminary to studying toxic glaucomas. Basing our experiment on the hypothesis of Leach

TABLE 1

Mean tonometry values between groups (G)

Group Means		No. of Observations	Standard of Error
G_I	20.6797	128	0.2961
G_{II}	22.3056	72	0.3947
G_{III}	19.7000	40	0.5296
G_{IV}	22.9125	80	0.3745

TABLE 2

Showing decomposition of the between groups mean square

Sum of Squares	Effect	Mean Square	Degree of Freedom	F Ratio
Due to	$(G_I - G_{III})$	29.2506	On 1	2.61
Due to	$(G_{II} - G_{IV})$	13.9597	On 1	1.24
Due to	$(G_I + G_{III} - G_{II} - G_{IV})$	378.7447	On 1	33.76

TABLE 3

SHOWING THE P/I, D/I, AND P/D VALUES OBTAINED FROM 22 RABBITS IN THE FOUR EXPERIMENTAL GROUPS FOR RIGHT EYE ONLY

Group I (Citral minus vitamin A)				Group II (Vitamin-A Deficiency)			
Rabbit No.	P/I	D/I	P/D	Rabbit No.	P/I	D/I	P/D
I/1	1.000	0.500	2.000	II/2	0.800	0.300	2.667
2	1.000	1.000	1.000	3	0.600	0.400	1.500
3	1.000	0.250	4.000	4	1.667	1.000	1.667
4	1.667	1.333	1.250	5	2.200	0.800	2.750
5	1.333	0.500	2.667	6	0.600	0.700	0.857
6	0.750	0.750	1.000				
TOTAL	6.750	4.333	11.917	TOTAL	5.867	3.200	9.441

Group III (Normal)				Group IV (Citral plus vitamin A)			
Rabbit No.	P/I	D/I	P/D	Rabbit No.	P/I	D/I	P/D
III/1	1.333	0.833	0.800	III/4	0.714	0.643	1.111
2	0.545	0.455	1.200	6	2.400	0.600	4.000
3	1.000	0.667	1.500	8	0.667	0.583	1.143
5	0.667	0.667	1.000	11	2.000	0.875	2.286
7	1.333	0.833	1.600	IV/1	1.333	0.625	2.400
10	1.200	0.700	1.714				
TOTAL	6.078	4.155	7.814	TOTAL	7.114	3.326	10.940

and Lloyd that with vitamin-A deficiency an even higher rise in tension occurs than with citral alone, we kept one group of rabbits on citral along with a vitamin-A deficient diet (Group I). We tried a wide range of dosage of citral, from 10 μg. to 52 mg., and performed tonometry and tonography at different times, from one-half to 24 hours after the administration of the last dose of citral, until we finally decided for the latter. We completely failed to obtain a clinical rise in tension over a period of weeks, although on statistical comparison of the four groups, Group II and Group IV showed slightly higher mean readings than Groups I and III; however, this was only significant statistically on decomposition of the "between groups mean squares"; the highest mean value was 22.91 mm. Hg as compared with the lowest mean value of 19.70 mm. Hg which could not be considered a clinical rise at all. It is further interesting to note that Group I which had chronic citral poisoning and vitamin-A deficiency showed a lower mean tension than the group which had no citral, but was on a vitamin-A deficient diet (Group II).

With straight tonometry yielding such un-

TABLE 4

ANALYSIS OF VARIANCE

Due to:	Degrees of Freedom	Sums of Squares	Mean Square	F Ratio
a. Showing the analysis of variance of the P/I values of Table 3				
Between means	3	0.4794	0.1598	1.94
Error	18	5.5675	0.3093	
TOTAL	21	6.0469		
b. Showing the analysis of variance of the D/I values of Table 3				
Between means	3	0.0206	0.06867	1.02
Error	18	1.2591	0.06995	
TOTAL	21	1.2797		
c. Showing the analysis of variance of the P/D values of Table 3				
Between means	3	2.4737	0.8246	1.07
Error	18	15.8597	0.8811	
TOTAL	21	18.3334		

TABLE 5

SHOWING THE MEAN VALUES OF P/I, M/I, AND P/D FOR THE FOUR EXPERIMENTAL GROUPS

	Variate	Group I	Group II	Group III	Group IV
P/I	No. of observations	6	5	6	5
	Mean	1.1250	1.1734	1.0130	1.4228
	Standard error	0.2251	0.2465	0.2251	0.2465
D/I	No. of observations	6	5	6	5
	Mean	0.7222	0.6400	0.6925	0.6652
	Standard error	0.1080	0.1183	0.1080	0.1183
P/D	No. of observations	6	5	6	5
	Mean	1.9862	1.8882	1.3023	2.1880
	Standard error	0.3832	0.4198	0.3832	0.4198

equivocal results, we tried tonography in the same four groups; there did not appear to be any difference in the behavior. Thus finally, the changeability test was applied; here also the four groups showed no significant differences one from another with regard to the ratios P/I, D/I, and P/D (table 4).

The only conclusion to be drawn on the basis of tonometry, tonography, and the changeability test is that citral did not have any significant effect on the intraocular dynamics of the rabbits utilized; nor did the presence or absence of vitamin A in the diet affect the result.

SUMMARY

1. A series of 36 rabbits divided into four groups was investigated to find out the effect of citral and vitamin A on the intraocular dynamics.

2. Neither citral nor vitamin A was found to have any significant effect on the intraocular pressure, coefficient of facility of outflow, or capacity of rabbits to vary the outflow resistance (changeability test).

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ACKNOWLEDGMENT

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REFERENCES

1. Becker, B.: Arch. Opth., **58**:871, 1957.
2. Berggren, L.: Acta Ophthal., **35**:5, 451, 1957.
3. Leach, E. H., and Lloyd, J. P. F.: Tr. Ophth. Soc. U. Kingdom, **75**:425, 1955.
4. ———: Tr. Ophth. Sc. U. Kingdom, **76**:453, 1956.
5. ———: Proc. Nutrit. Soc., **15**:15, 1956.
6. Linnér, E.: Brit. J. Ophth., **52**:38, 1958.
7. Moore, T.: Vitamin A. London, Elsevier, 1957, p. 539.

A RETINOGRAPHIC SURVEY OF FUNDUS CHANGES

The arteriovenous crossing phenomena

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The recognition of the study of the ocular fundus changes as a valid diagnostic aid for systemic hypertension and allied diseases goes back almost to Helmholtz's invention of the ophthalmoscope during the 19th century. By the turn of the century, only pathologic changes involving the retinal tissue were recognized as diagnostic signs for the retinopathies.

Late in the 1920s, pathologic alterations in the retinal vessels began to be accepted as valid signs—the more commonly studied being general constriction of the arterioles with acute branching angles, modifications in size, color, or intensity of the vascular reflexes; modifications in the relations between the arteriolar and venular diameters; the various degrees of caliber changes either of whole or localized segments of arterioles, the arteriole spasms; the sheathing of arterioles and venules; dilation and stasis of the venules; the crossing phenomena.

Although there is already a great degree of uniformity in the denomination of these signs, there is still by no means a certainty that different authors really mean the same things when using the same names. The descriptions and interpretations of these signs are even less in accord. In almost every issue of ophthalmic periodicals appear new articles with different points of view.

Most of the knowledge of these signs was acquired by purely ophthalmologic research, usually only with the ophthalmoscope, measurements being taken either by projection of scales on the fundus or by simultaneous comparison with normal eyes. Only in recent times have the optical techniques been developed to a point where the clinical ophthalmologist can avoid the limitations imposed by the ophthalmoscope. The Hruby lens makes clinical slitlamp examination of the fundus easy, and the recently developed electronic-flash retinograph brings to fundus photography a surprising degree of amplification, detail, and contrast. The Zeiss instrument is so constructed that it allows valid measurements between different pictures. These are the more modern techniques for studying the fundus.

In order to study pathologic vascular alterations in the fundus, using these new tools in addition to the systematic use of the ophthalmoscope, for a period of more than one year every hypertensive patient referred for fundus examination was studied at the slitlamp in addition to the usual ophthalmoscopic examination. Throughout this period every patient examined for whatever reason was studied in the same way whenever any abnormal fundus finding was encountered in routine examination. Retinographs were taken in every case in which the findings warranted it. A collection was started of pictures so obtained and these were correlated with clinical data of each case as far as available. Of several hundred cases examined, 86 form the material for this report.

Whenever possible, black and white as well as color pictures were taken from each important sector. Occasionally, extreme uncooperativeness of the patient or the impossibility of getting a clear image of the fundus, due either to haziness of the media or inability to dilate the pupil, made retinography impossible. The black and white photographs were originally thought of only as controls, chiefly to verify possible artefacts in the color pictures. (Moreover, developing of colored pictures is done in the United States and so prints are available only after some weeks, while the black and whites are developed locally without delay.)

To my great surprise it was found that many fundus changes that are almost invisible in the color photographs are easily seen

in the black and white ones. Careful re-examination, principally with the red-free slitlamp, showed that these changes really existed to the extent shown in the black and white retinographs. The explanation for this seems to be that the black and white film is far less sensitive to the red light and so able to record details that are normally blanketed by the wealth of red light reflected from the retina. Even so it was necessary to use special high-contrast developing and printing processes to bring out these details to their full extent.

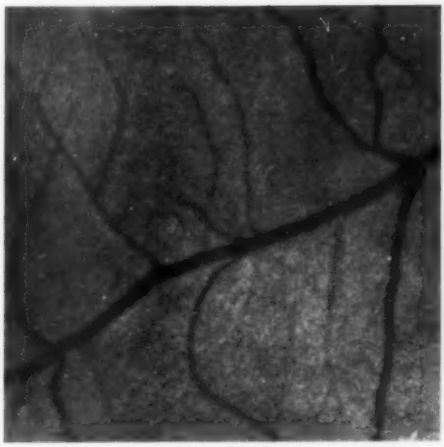
Due to this fact and to the ease of reproduction, only black and white retinographs appear in this report, even though the corresponding colored ones are available in most cases. Out of the wealth of data obtained during this fundus study, only those concerning the arteriovenous crossing phenomena were chosen for this report.

Apparently Gunn (1892) was the first to describe the crossing phenomena. At the time he considered them signs of hypertension, whereas fundus alterations involving the vessels were considered as purely arteriolosclerotic. Gunn started the discussion that, on many points, still continues.

The works of Salus called attention to the importance of these signs so that many authors today call them the Salus-Gunn signs. Originally attention was given only to those changes occurring where the artery crosses over the vein (as seen in the ophthalmoscope)—the direct crossing. The modifications of the inverse crossing (where the vein crosses over the artery) were pointed out only recently by Biro (1956). His report represents the only major ophthalmic contribution to this subject in recent years.

In the present study an attempt was made to establish how closely these signs resemble descriptions of them, to interpret them and to correlate them to the general condition of the patient. A search was also made for not yet published modifications that were sufficiently clear-cut to merit attention.

The direct crossing phenomena are divided into arching and nicking types (Salus):



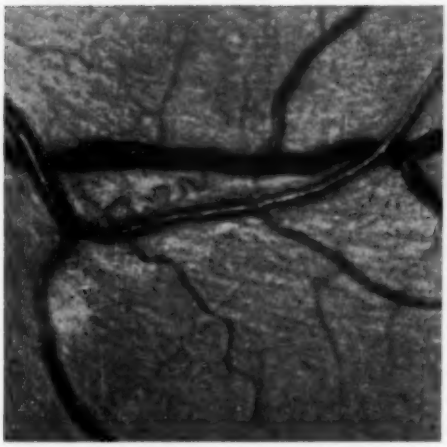
Retinograph 1* (Behrendt). A 41-year-old white man had a history of increasing hypertension for years, with sporadic exacerbations. At the moment of retinography, his blood pressure was 18/13 cm. Hg but he reported a past blood pressure of 22/14 cm. Hg. Illustrated is an apparently pure nicking phenomenon in the perimacular vessels. Note the presence of a small degree of attenuation.

The nicking type is a change in the direction of the vein, this change varying from nothing more than the formation of a very small step at the crossing to a change in course arising several arterial diameters away from the crossing and extending as far beyond. A form in which the vein shuns the artery, so to speak, is also considered (fig. 1).

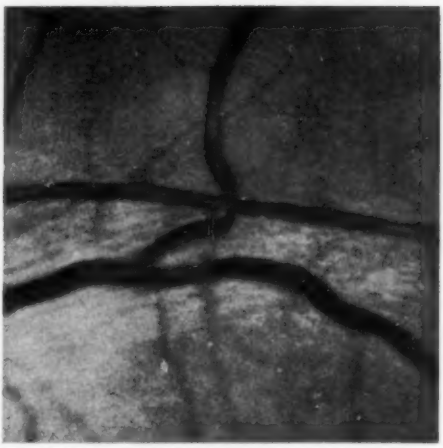
The arching type shows a modification in which a noticeable attenuation or distal engorgement of the vein extends up to several arterial diameters from the crossing (fig. 2).

In my series, even the most clear-cut nickings showed a certain attenuation of the vein in the immediate neighborhood of the artery, as can be seen in a close examination of Retinographs 1, 2, 3, and 4, though these at first glance appear to be purely nickings. This difference between my observations and those of Salus may arise from different

* Each retinograph is enlarged up to ×40. In order to avoid artefacts, no retinograph was retouched.

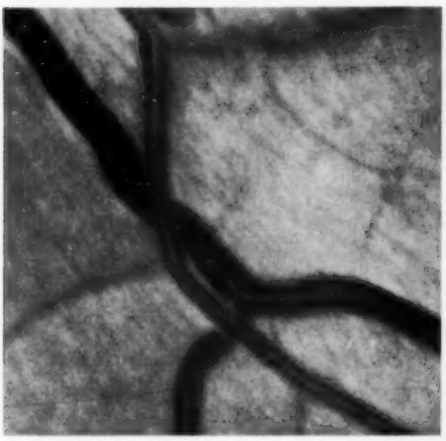


Retinograph 2 (Behrendt). A rather obese 53-year-old white woman, for years has had a blood pressure of 17/11 cm. Hg but follows no treatment. Her only subjective complaint was an occasional headache. Urine, negative. Note nicking of the principal veins, the ever-present attenuation, the small but noticeable changes in the retina around the crossing.

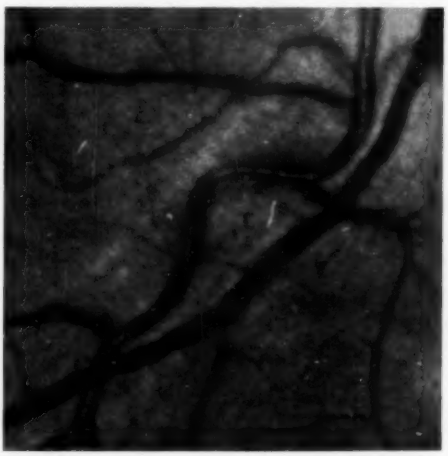


Retinograph 4 (Behrendt). The same patient and findings as in Retinograph 3.

methods of examination. Since the ophthalmoscope shows far less of the arterial walls than the retinograph, the attenuation of a vein can be seen more easily by retinography. Salus holds that nicking can be a precursor to arching but says that arching is always hypertensive while nicking may be only arteriolosclerotic. He thus makes a rigid distinction between the two types. My finding of attenuation in every case of nicking, together with finding arching in a case long under treatment for hypotension (retino-



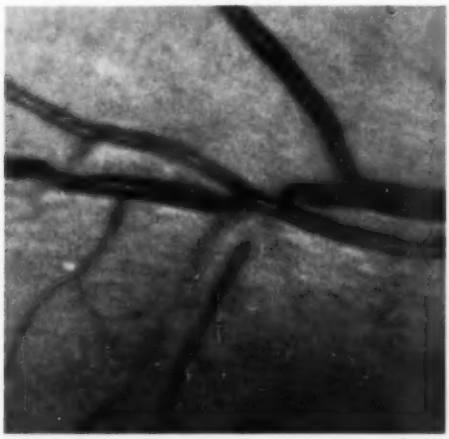
Retinograph 3 (Behrendt). A rather obese 47-year-old white man had hypertension of long standing and not well-compensated heart trouble. He follows no treatment. Nicking of the principal veins. Note the ever-present attenuation and the small but noticeable changes in the retina around the crossing.



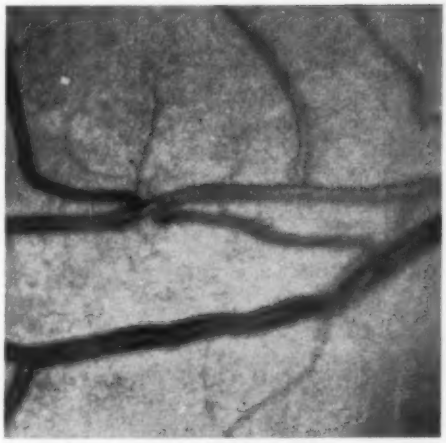
Retinograph 5 (Behrendt). A 55-year-old white woman had been under treatment for hypotension for a long time. When the retinograph was taken blood pressure was 12/8 cm. Hg. Beginning of a classical arching phenomenon. Note changes in the retinal tissue.

Fig. 1 (Behrendt). Progressively more marked degrees of nicking. (After Sallus.)

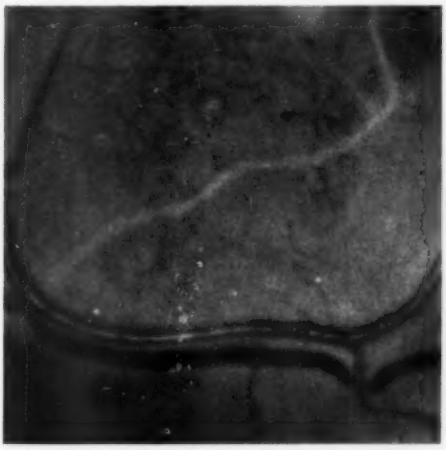
Fig. 2 (Behrendt). Progressively more marked degrees of arching. (After Salus.)



Retinograph 6 (Behrendt). A 45-year-old white woman had long been under treatment for hypotension at times so severe she was confined to bed. Blood pressure at retinography was 11/7 cm. Hg. The arching phenomenon is illustrated. Note how the whole bifurcation of the vein disappears under the crossing.



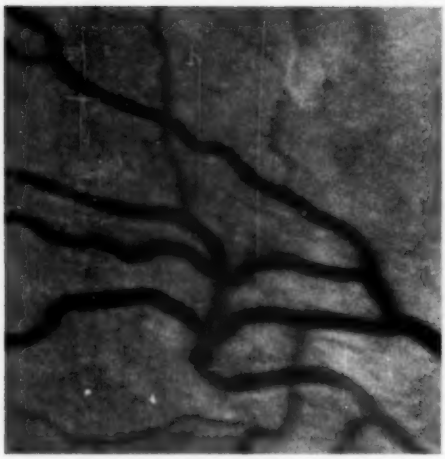
Retinograph 7 (Behrendt). This 50-year-old white man had a long history of hypertension, with a cerebrovascular accident two years ago. Blood pressure was 24/14 cm. Hg. Marked archings, with noticeable changes of the retina in the area of crossing.



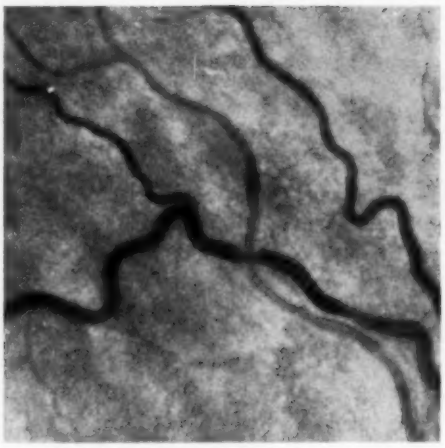
Retinograph 8 (Behrendt). A rather obese 50-year-old white woman, complained of dizziness and headaches. Her blood pressure was 13/9 cm. Hg. She had no history of hypertension. Marked archings and noticeable changes of the retina in the area of crossing.

gram 6), seems to cast doubt on the validity of this fundamental distinction.

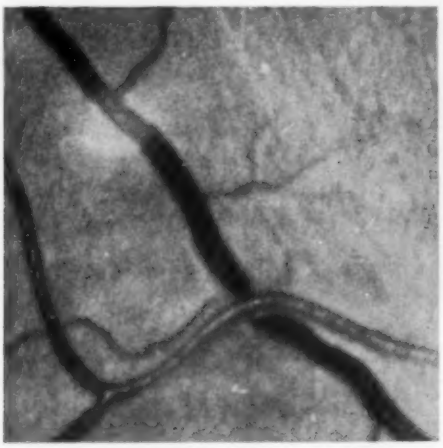
In the arching phenomenon, attenuation to several diameters from the crossing (retinograms 9 to 15 and 17, 18, 19) could not be found. Whether this is due to the reported cases not showing them is not known; however, it is worth while to point out that Retinograms 18 and 19, from severe cases of hypertension, were taken shortly before the death of the patient. On the other hand it is easy to see from Retinograms 5, 6, 7, and 8 that there is a whole range of transitions in these two classic forms of the crossing phenomena which seems to invalidate any clear separation.



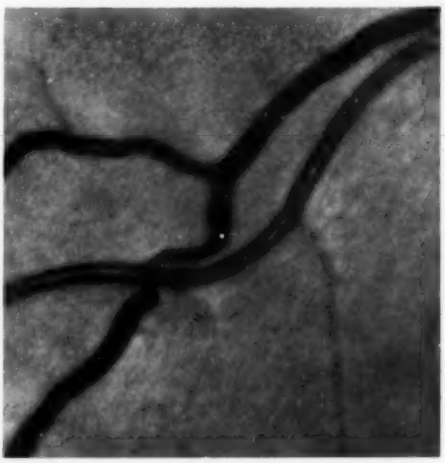
Retinograph 9 (Behrendt). A 55-year-old man with a long history of hypertension and beginning heart failure with dyspnea. He had followed almost no treatment. Blood pressure was 24/13.5 cm. Hg. Marked archings and noticeable changes of the retina in the area of crossing. (See also Retinograph 26.)



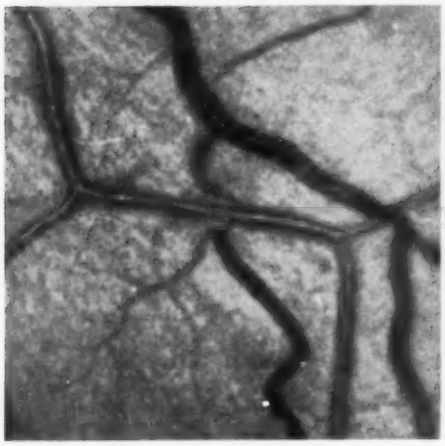
Retinograph 10 (Behrendt). Same patient and same findings as in Retinograph 9.



Retinograph 11 (Behrendt). Although a known hypertensive for at least 10 years, this 54-year-old white woman had followed only sporadic treatment. Blood pressure was 18/10.5 cm. Hg. Intense arching phenomenon. Note the more marked involvement of the retina in the area of crossing. (See also Retinograph 24.)

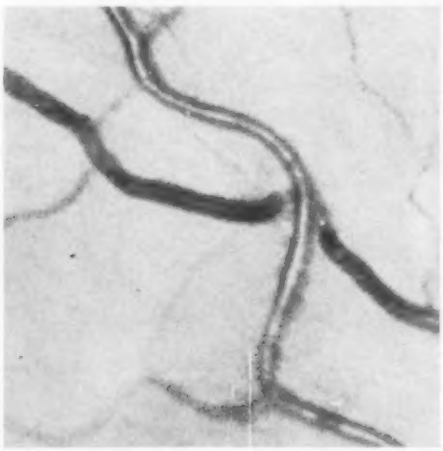


Retinograph 12 (Behrendt). A 48-year-old white woman, although frequently examined for chronic bronchial asthma, had had no signs of hypertension until two years ago when her blood pressure rose to 20/14 cm. Hg. Since then she has been under mild treatment with rauwolfia alkaloids but the diastolic pressure never goes below 10.5. This patient's mother died of hypertension which had led to total blindness of one eye due to intense vitreous hemorrhage; vision in the other eye was reduced due to advanced arteriosclerosis and macular degeneration. Intense arching phenomenon. Marked involvement of the retina in the area of the crossing. (See also Retinographs 13, 14 and 23.)

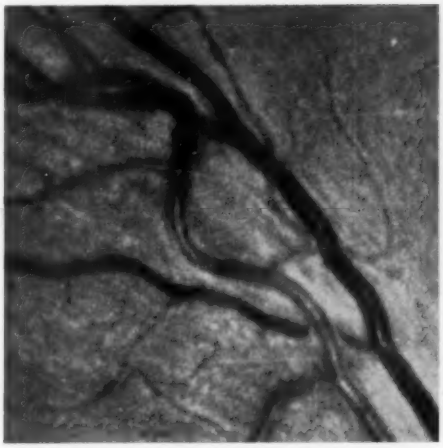


Retinograph 13 (Behrendt). Intense arching phenomenon, with marked retinal changes in the area of crossing. Same patient as in Retinograph 12.

It is also interesting to note an associated change in which the vein is only touched but not crossed by the artery, yet is similarly attenuated (retinogram 17). The occurrence of this phenomenon, first described, as far as could be learned, by Geller, seems to be closely related to the crossing phenomena and has to be considered with them when considering their significance and etiology.

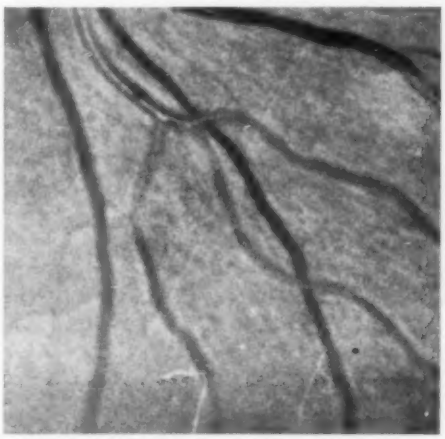


Retinograph 14 (Behrendt). Intense arching phenomenon and marked retinal changes in area of crossing. Same patient as in Retinograph 12.

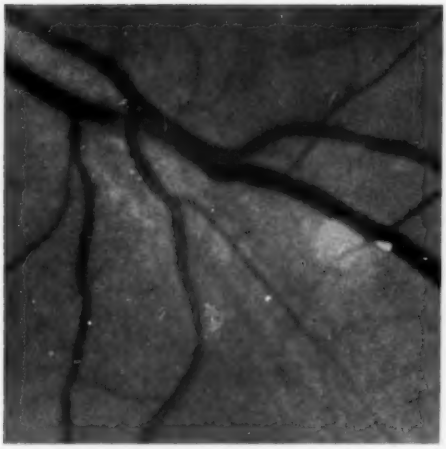


Retinograph 15 (Behrendt). A 35-year-old obese Negress, with a long history of hypertension. Intense arching phenomenon. Note the marked involvement of the retina in the area of crossing.

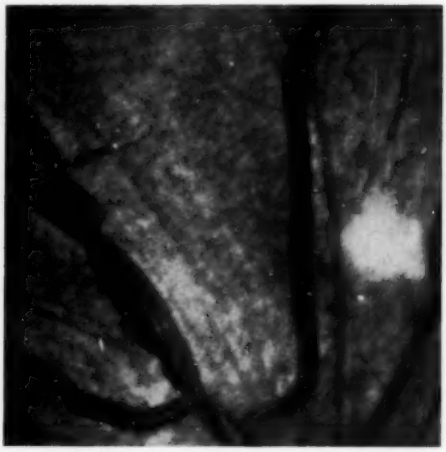
The indirect crossing phenomenon, as described by Biro, only involves a change in direction of the vein while crossing over the artery. His descriptions, ranging from a small arching of small veins over larger arteries (found by me in many cases clinically normal and showing no other modifications



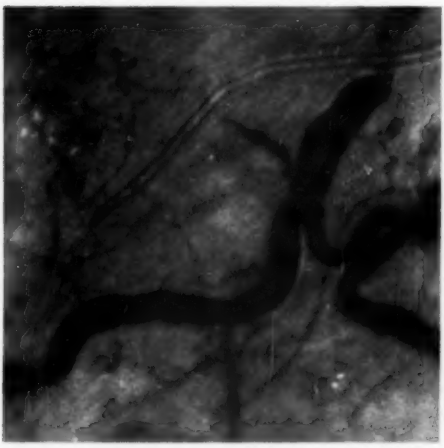
Retinograph 16 (Behrendt). An area adjacent to that shown in Retinograph 15. The artery is a branch of the same major subdivision of the central artery. Note the absence of changes at the crossing.



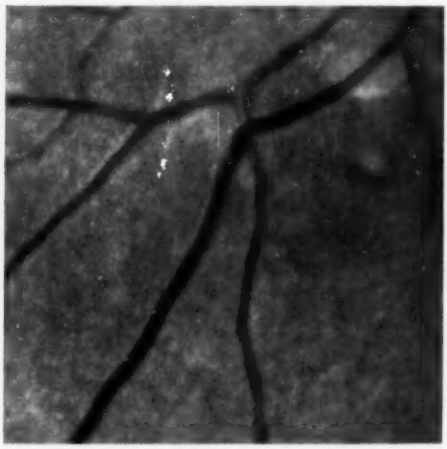
Retinograph 17 (Behrendt). A 58-year-old man who had had hypertensive crises for years, with blood pressure of 23/15. Between crises the blood pressure was normal. At the time of retinography the blood pressure was 15.5/9.5. Changes occur where the artery and vein are contiguous.



Retinograph 18 (Behrendt). Two years ago this 38-year-old Negress had had an episode of cardiac failure which had been compensated. At that time she was reported as having a KW2 type fundus. Shortly after the present hospitalization for hypertension, and at the moment of retinography, she died of hypertensive cardiac failure. The retinograph shows the same arching-type changes occurring in a rather severe retinopathy. Note that, although the other changes are marked, the pattern of the crossing is the same.



Retinograph 19 (Behrendt). This 43-year-old man had rapidly increasing symptoms—headaches, dizziness, heart and visual failure. Nine months after these symptoms began he sought aid. At this time blood pressure was 28/16 cm. Hg. Under careful treatment and hospitalization, blood pressure was reduced to 14/9 cm. Hg. Two months after leaving the hospital, he was readmitted with blood pressure of 23/17 cm. Hg. This time it could be reduced to only 19/10 cm. Hg. He died four weeks later of a cerebrovascular accident. This retinograph also shows the same arching-type of changes at the direct crossing occurring in a severe retinopathy. Although the other changes are more marked, the pattern of the crossing is the same.



Retinograph 20 (Behrendt). A 54-year-old white man with normal tension. The indirect (or inverse; the terms are synonomous) changes at the crossing are not very marked.

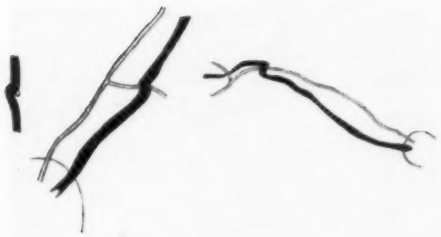
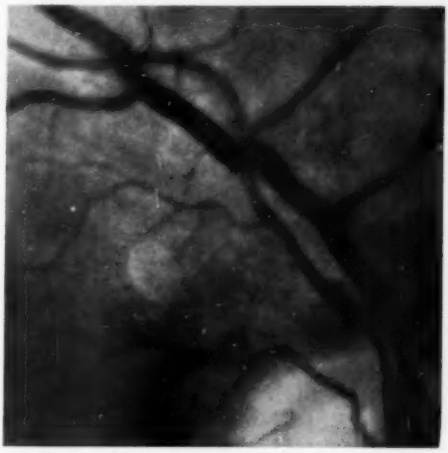


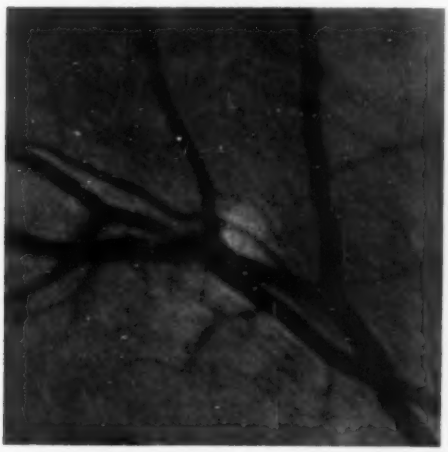
Fig. 3 (Behrendt). Two forms of inverse crossing changes, as described by Biro. Without attenuation. (Left) Note the strange similarity to Retinograph 22.



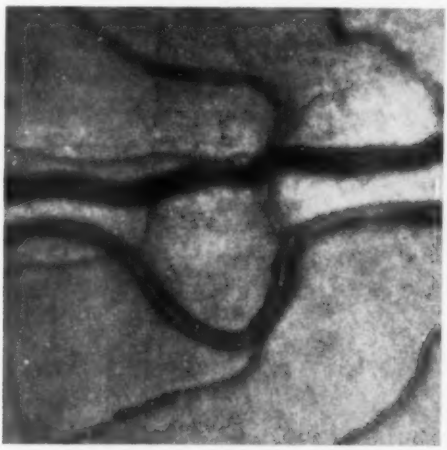
Retinograph 22 (Behrendt). For several years, this 58-year-old white man had a history of hypertension. At the moment of retinography, blood pressure was 18/10 cm. Hg. The inverse changes at the crossings are more marked.

of the vessels) to severe changes occurring where large veins cross over large arteries, speak of alterations only of the direction and never of the caliber (that is, an attenuation) of the vein. I was able to confirm his descriptions in every detail. Note the similarity of Figure 3 (from Biro) and Retinograms 21, 22, 23, 24, and 25.

I was also able to identify an indirect crossing phenomenon, to my knowledge not yet described. In it the important feature was not the change of the direction of the vein while crossing over the artery but the change of its caliber (attenuation). This attenuation may range from very slight to so marked that the first impression is that the vein is actually interrupted and passing beneath the artery rather than over it; it is simply extremely attenuated (retinograms 26 and 27 and fig. 4). This phenomenon is, so to speak, the reverse of the arching phenomenon as classically described, whereas



Retinograph 21 (Behrendt). Over a long period, this 53-year-old man had had frequent episodes of hypotension. Here also the indirect (or inverse) changes at the crossing are not marked.



Retinograph 23 (Behrendt). The inverse changes at the crossing are moderately marked. See Retinograph 12.

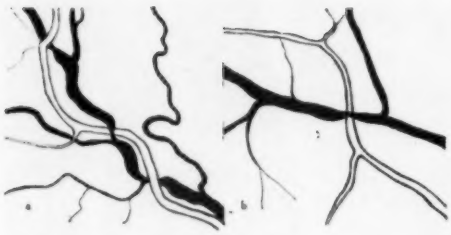


Fig. 4 (Behrendt). (a) Inverse phenomenon with attenuation of the vein (Behrendt). This drawing was made after Retinograph 26. (b) Another form of the inverse phenomenon with attenuation of the vein. This drawing was made after Retinograph 27.

the inverse phenomenon, as described by Biro, would be the reverse of the nicking phenomenon, as usually described (without attenuation).

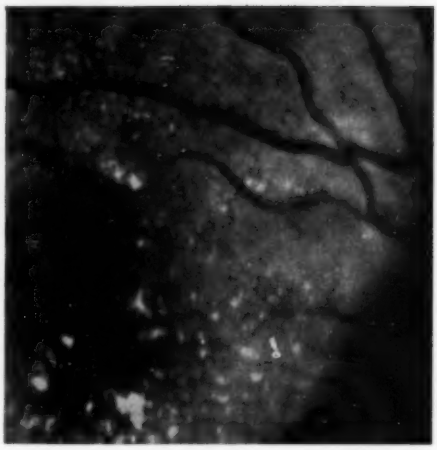
Although it is difficult to give a really well-founded etiologic explanation of these phenomena by purely ophthalmic means of research, such as those used in this study, it would seem that purely mechanical theories of compression or rendering invisible by occlusion are not sufficient. Besides the well-known objection that there are changes so far away from the crossing that they can hardly be attributed to compression, attention should be called to the following facts:

1. There is change around the crossing that not only involves the vessels but also the retina.

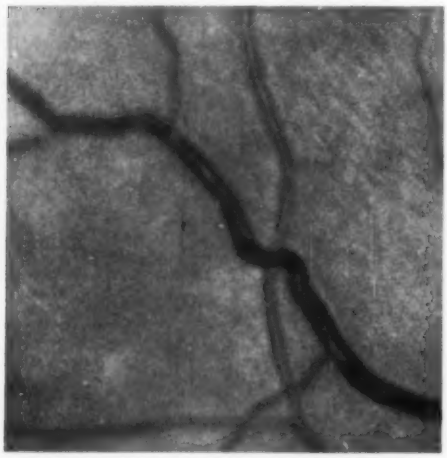
2. Similar changes occur in the phenomenon described by Geller in which it seems doubtful compression could be invoked at all. (Ophthamoscopically, these changes are often difficult to see to their full extent but can be seen in the black and white retinographs and in the red-free slitlamp examination.)

3. Identical modifications also occur when the vein is crossing over the artery. How could the artery compress the vein against the vitreous?

4. The phenomena are by no means as symmetrical as is usually described. Espe-



Retinograph 25 (Behrendt). Eight years before his death this 42-year-old white man had increasing headaches, dizziness, nausea, vomiting, pains in his left arm, diminishing vision, and loss of consciousness. Three months before his death he was hospitalized with a blood pressure of 24/14 cm. Hg. Under treatment it was possible to reduce the pressure to only 17.5/9 cm. Hg. Blood urea was high during the whole period, at times reaching to 150 percent. Note the inverse crossing change in this case of intense retinopathy. As in Retinographs 18 and 19, the marked retinopathic changes are more arresting than those at the crossing. (Note also that in none of the retinographs from 20 through 25 is there an attenuated vein.)

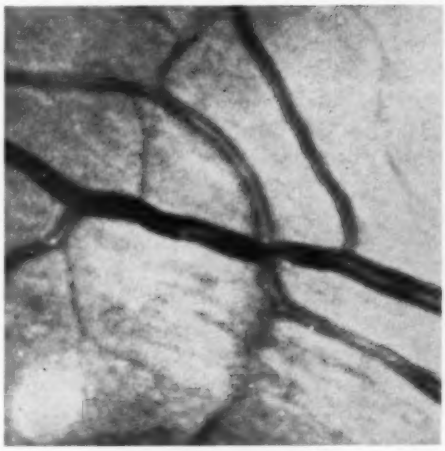


Retinograph 24 (Behrendt). Also moderately marked are the inverse changes at the crossing. See Retinograph 11.

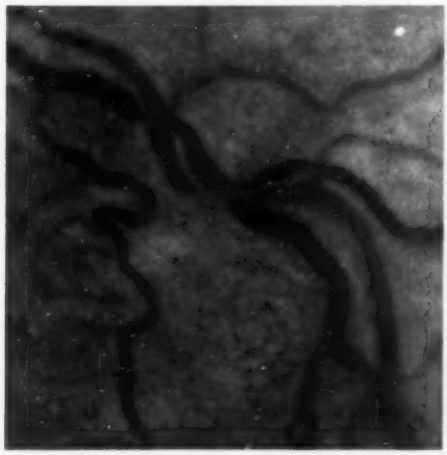
cially in the cases of arching where the vein is not only attenuated but also forms a real arch, there are marked variations.

Even though a complete explanation cannot, as yet, be offered, any theory that tries to explain the crossing phenomena should attempt an explanation for these observed findings. The theory I feel comes closest to complete explanation is that of formation of phlebo-arterial alterations at the crossing or at the points where artery and vein are contiguous. This would cause the attenuation as well as the change of the direction. Since only a point of contact between the vessels is needed this would also explain the changes of the inverse crossing. As a biologic process it would likely be assymmetric. Further, it also accounts for the occurrence of the changes along the vessels, or of the retinal tissue, at a greater distance from the crossing.

It is very likely that compression is a provocative agent in the formation of these phenomena. This would explain why changes in the direct crossing are found more frequently than in the inverse, and also why the changes of direct crossing are more frequent in hypertensive patients than in others.



Retinograph 27 (Behrendt). A 42-year-old Negro had a long history of hypertension. Headaches and dizziness appeared, as well as renal insufficiency to a degree compensated by polyuria. Finally, vision diminished, blood pressure then being 17/11 cm. Hg. It was possible to reduce the blood pressure to normal levels by careful treatment with rauwolfia and veratrum alkaloid. His blood pressure has now been normal for over 12 months. The retinograph shows a marked inverse crossing with extreme attenuation of the vein which (due to attenuation) seems at first sight to pass below (direct crossing) and not over the artery.



Retinograph 26 (Behrendt). An inverse crossing with attenuation at the side of a typical arching. (See Retinographs 20 through 25 in which there is no attenuation of the vein.) Same patient as in Retinographs 9 and 10.

In my fundus observations, the crossing changes usually were not distributed evenly over every crossing. The rule seems to be that rather well-advanced changes may be found along side of almost normal ones. Usually the altered crossings affect only some branches of the arteries, which are also sites of other modifications. Other branches are quite normal. Thus, for instance, Retinograms 15 and 16 not only are from the same eye but even from branches of the same subdivision of the central artery. Retinogram 15 shows modifications even where very small arterioles cross the principal vein, while in Retinogram 16 no changes can be found at all.

The only exception to this rule I was able to find was the case shown in Retinograms

12, 13, 14, and 23 where every crossing is not only modified but even modified to approximately the same degree. It is noteworthy that, although the patient had complained for the last two years only of general hypertensive symptoms, earlier examinations revealing no changes, this patient's mother suffered from and died of hypertension, having pathologic alterations of the ocular fundus that led to massive vitreous hemorrhage in one eye and macular degeneration in the other. This case, being well documented, suggests the hypothesis that there is some intrinsic factor contributing to the development of these fundus changes.

Touching the old problem of the relation of these changes to hypertension, I was not able to find a clear-cut relation of any of the crossing phenomena to hypertension itself. On the contrary, I found many cases of small or no changes of the crossings or even of the fundus in patients with long and well-corroborated histories of hypertension, for example, the case shown in Retinograms 1 and 2. On the other hand I was able to find cases of well-marked crossing phenomena in normotensives or even in persons with a long history of hypotension. The case shown in Retinogram 6 has long been under medical care for hypotension.

This seems to indicate that hypertension by itself is not the cause of the changes at the crossing. On the contrary it seems that some vascular process is involved which can be precipitated by hypertension but may also appear under other circumstances. This agrees closely with the observations of Sauter on arteriolosclerotic vessel changes in the fundus of hypotensive patients, and with Leishman's theories and observations about the fundus changes caused by systemic hypertension.

It is also noteworthy that the conclusions drawn from the incidence of changes in hypertensive, normotensive, and hypotensive patients agree closely with those drawn from purely morphologic ones. All this does not invalidate the existence of a clear-cut hypertensive retinopathy in cases where the crossing changes occur along with and are overshadowed by other more apparent and compelling alterations which dominate the evaluation of the whole picture. Finally, this theory still agrees with the fact that the crossing changes are more commonly found in hypertensive patients and it is supposed that hypertension is one of the agents provoking these changes.

Summary

A survey was made of persons suffering from hypertension and allied systemic disorders, and also of apparently normal persons who showed retinal changes usually associated with these disorders. In addition to a careful ophthalmoscopic examination, retinographs were taken and all available clinical data were collected. From this material, only the crossing phenomena are discussed in this paper. In addition to comparison of the known descriptions with the photographic evidence, a new sign is described. The article undertakes to show that there is, as yet, no certain relation between systemic hypertension and the nature or intensity of the crossing changes.

Caixa Postal 878.

References

Biró, I.: Verkehrte Gefaesskreuzungsphaenomene am Augenhintergrund hypertonischer Kranken. Klin. Monatsbl. f. Augenh., **128**:672-678, 1956.

Geller, P.: Beitrag zum ophthalmologischen Bild des Fundus hypertonicus. Klin. Monatsbl. f. Augenh., **133**:570-572, 1958.

Leischmann, R.: The eye in general vascular disease. Brit. J. Ophth., **41**:641-701, 1957.

Michel, J.: Lehrbuch d. Augenh., 1890, pp. 451-453.

Salus, R.: Diagnosis of arteriosclerosis. Am. J. Ophth., **45**:81-92, 1958.

Sautter, H.: Die Arteriosclerose des Augenhintergrunds. Klin. Monatsbl. f. Augenh., **127**:641-657, 1955.

NOTES, CASES, INSTRUMENTS

NEW PIGMENT FOR CORNEAL TATTOOING

Report of three cases

Sherman B. Forbes, M.D.
Tampa, Florida

It is my impression that ophthalmologists have been disappointed frequently in the results they have obtained from tattooing the cornea with the more common pigments, that is, India ink, lampblack, gold chloride, and so forth. It therefore seems worthwhile to report my experience with a new pigment that has given highly satisfactory results in three instances.

During the last year, I have had three cases in which tattooing was definitely indicated. Before deciding on the pigment, I discussed the matter with a pharmacist. He consulted a tattoo artist in the city, who informed him that for skin tattooing purified animal charcoal was being used. The pharmacist worked on from there and made a paste of this substance, incorporating for at least a bacteriostatic action both phenol and alcohol according to the following prescription:

Purified Animal Charcoal	3 ii
Phenol	1 gtts.
Grain Alcohol	1 cc.
Distilled Water	4 cc.

Add the liquid to the purified animal charcoal until a workable consistency is obtained.

In all three cases, the technique consisted of using a trephine to remove enough tissue from the cornea to get well into the substantia propria. It was then only necessary to rub this paste on the denuded area a few times to obtain adequate pigmentation. The globe showed little reaction to this procedure. Fourteen months have elapsed in the first case, 10 in the second, and six in the third, with the results continuing to be most satisfactory. The tattooed area is not a solid black, but has a somewhat striped appearance; however, there is definitely sufficient pupil blackening to overcome the cosmetic defect.

This pigment appears to be worthy of a trial by other ophthalmologists in order to obtain a thorough evaluation.

409 Citizens Building.

Footnote

The pigment formula was worked out by L. L. Kilgroe, Jr., of the William Parr Drug Company, Tampa, Florida.

NEW DUAL-END INSTRUMENT*

For basal peripheral iridectomy on the dilated pupil

Richard J. Broggi, M.D.
Worcester, Massachusetts

An even-bordered, well-placed peripheral iridectomy in the presence of a dilated pupil, such as is induced and encountered in "round pupil" cataract extraction, may be a rather difficult task. If the pupil is dilated, it may be difficult to judge the size of any cut in the iris and difficult to grasp a truly peripheral portion of the iris for excision, especially in the presence of a scleral shelf of even moderate size.

For ease and efficacy in the performance of a basal, peripheral iridectomy, it would seem as if three hands were necessary; one with forceps, temporarily to retract some of the dilated iris tissue which is crowded into the angle, another with forceps to grasp a more peripheral portion of the iris, and a "third hand" with scissors for excision of a truly basal portion of iris.

It occurred to me that such a "third hand" effect might be accomplished with a dual-end, spring-handled instrument (fig. 1*), with a smooth iris forceps on one end and iris scissors (McClure-type blades) on the

* This instrument was made for me by the E. A. Storz Instrument Company, 4570 Audubon Avenue, Saint Louis 10, Missouri.

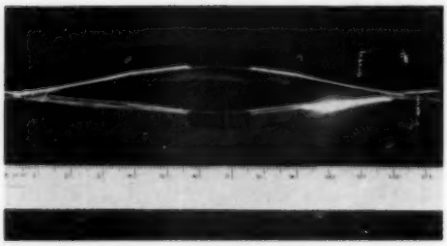


Fig. 1 (Broggi). This instrument is more conveniently used if the handles are sprung laterally to a wider position so that the instrument assumes more of a diamond shape than is shown.

other end. The instrument is used in the following manner:

While the corneal flap is elevated by the assistant, the forceps end of the instrument is used to retract gently a portion of the iris centrally in the meridian of the proposed iridectomy. A second pair of very delicate iris forceps is then used to grasp a tiny, tenting fold of a peripheral portion of the iris which is sharply torn from its base for two to three mm. by a short and quick tug, just after removal of the first forceps.

The scissors end of the double-end instrument, which has been inverted in the hand, is then used to excise as large a portion of the iris base as is deemed optimum by appropriate spacing and angling between the forceps and the scissors blades. It is preferable if the separate iris forceps has smooth blades from which the excised iris may be easily brushed, especially if a second iridectomy is planned. If toothed forceps are used, there may occur the nuisance of having to interrupt surgery and disengage the excised iris from the teeth of the instrument before performing the second iridectomy. Of course, there is also less risk of damage to underlying structures with the smooth forceps.

The act of inverting the double-end instrument in one hand is simple and after a few trials almost as familiar as inverting a lead pencil for the purpose of using the eraser. Moreover, it can and should be done without removing the hand or eyes from the operative field. However, for the greatest ease and to avoid any risk of dropping the instrument, the inversion should not be hurried. Usually, the portion of dilated iris previously grasped with the forceps end of the instrument will gather back or even spring back into the angle but any hindrance is easily avoided by slight elevation of the basal portion of iris with the separate forceps.

This instrument has facilitated peripheral iridectomy on the dilated iris by providing the means for a smooth technique in routinely obtaining basal iridectomies which are precisely placed, small and invariably even-bordered. It has been satisfying to have such a good-appearing and functionally adequate type of iridectomy and comforting to know that, even if it becomes necessary or desirable to dilate the pupil postoperatively, there is much less danger of closure than may be the case with a ragged iridectomy or an iridotomy.

36 Pleasant Street (8).

HYDRODYNAMIC CATARACT EXTRACTION

EDWARD I. LIPSIUS, M.D.
ALVIN W. HOWLAND, M.D.
I. S. TASSMAN, M.D.
AND
JOSEPH HALLETT, M.D.
Philadelphia, Pennsylvania

One of us (E.I.L.) became interested in the removal of the dislocated lens by irrigation and successfully performed this in four cases. This prompted consideration of its use in cataract extractions where the lens was in a normal situation. The original interest was aroused at a discussion by Dr. K. Lindner at Wills Eye Hospital in 1949.

Recently an article by F. H. Verhoeff[1] was found which described a case in which a cataract fell back into a fluid vitreous. By use of irrigation and a loop, he was able to deliver the lens. He stated that the procedure

might be effective in certain cases of cataract in which the vitreous is normal.

Use of irrigation in normal cataract extraction was further suggested when Dr. Derrick Vail[2-4] emphasized the presence of hyaloid-capsular adhesions, which can tear the posterior capsule of the lens or the anterior hyaloid of the vitreous during lens extraction. This was called the "adhesion syndrome" by Reese and Wadsworth.[5]

It was felt that a stream of fluid between the posterior capsule of the lens and the anterior face of the hyaloid might sever these adhesions without tearing the lens capsule or hyaloid, and also separate the zonule at the same time. Extraction of the normal lens in rabbits was tried by means of irrigation. The zonule was stripped at the 12-o'clock position and the stream of fluid was directed between the lens and the hyaloid. The zonules in rabbits, however, are very strong and some difficulty was encountered. Nevertheless, in two out of five cases, the lens was delivered without loss of vitreous. In three cases there was loss of vitreous. Because of the unfavorable percentage, it was not deemed feasible to try this procedure on human eyes, even though human zonules are weaker than those in rabbits.

With Barraquer's[6] introduction of alpha chymotrypsin for separation of the zonule, it was felt that removal of the lens by irrigation might be successful because the zonule would now be dissolved and any strands left could be separated by mild irrigation. The regular technique described by Barraquer was used for solution of the zonule with alpha chymotrypsin and complete iridectomy was used in all cases. A Troutman cannula should be used for the injection of the alpha chymotrypsin solution.

A lens spoon is applied at the 6-o'clock position, with gentle pressure being used straight downward anteroposteriorly as a test to see if the zonule is dissolved. If the equator of the lens at the 12-o'clock position rises above the incision when this is done, we know the zonule has been dissolved.

An irrigator is now used at the 12-o'clock position, slightly depressing the proximal edge of the cataract incision (the surgeon being in the usual position at the head of the patient). The irrigator just touches the posterior capsule of the lens behind the equator with the tip of the irrigator just out of view. The irrigating solution can be normal saline or more preferably Ringer's solution. The solution is directed by the irrigator horizontally through the retrolental space toward the 6-o'clock position. As the fluid is gently forced between the posterior capsule and the hyaloid, the spoon is used at the 6-o'clock position to break any remaining zonule and to guide the cataract out, exactly as it is done in extracapsular extraction.

This method of cataract extraction was performed on 12 patients, whose ages ranged from 36 to 81 years. There were no complications at the time of operation. There were some postoperative complications.

One patient on the first postoperative day had a wound separation at the 12-o'clock position between the track sutures. Another suture was then placed at this site and vision was 6/9 four months later.

Two cases showed more striate keratitis than normal. One of these was that of a 36-year-old woman in whom repeated extraction was attempted by forceps and erisophake but the zonule could not be broken. It was suggested that alpha chymotrypsin be used and the lens was irrigated out with no difficulty. The corneas in both cases of more than average striate keratitis cleared up without opacity and a good fundus view could be obtained in each eye.

The experience with the lens capsule is interesting. One would expect to get intracapsular extractions in 100 percent of the cases. However, one case considered as extracapsular showed no postcapsular membrane after surgery. It was concluded that, as the zonule was dissolved, the capsule, being loose, was washed out with the lens. The other case was considered to be intracapsu-

lar but an opacity either of the face of the vitreous or a posterior capsule of the lens presented itself. It was difficult to be certain. Needling was necessary.

This method is not being advocated at this time as the best way to do a cataract extraction, since it has been used on only 12 occasions. The purpose at this time is to report that it is mechanically possible to remove a cataract by irrigation after the zonule has been dissolved by alpha chymotrypsin. This can be accomplished without loss of vitreous. The lens undoubtedly in some cases could be delivered by external pressure alone, without any irrigation. We are certain, however, that irrigation is a valuable mechanical aid.

Conclusion

This is a preliminary report to demonstrate that a cataract can be extracted by irrigation after using alpha chymotrypsin to dissolve the zonule. It is emphasized at this time that a complete iridectomy be done in all cases. Also, a blunt needle should be used for the introduction of the alpha chymotrypsin. A spoon for external pressure rather than a hook is also recommended.

319 South 16th Street (2).

Footnote

After this work was started, it was noted that K. Hruby advocated simple expression of the lens after zonulysis. (Hruby, K.: Expression of cataract after zonulysis with trypsin. Klin. Monatsbl. f. Augenh., **134**:527-531, 1959.)

References

1. Verhoeff, F. H.: A simple and safe method for removing a cataract dislocated into fluid vitreous. Am. J. Ophth., **25**:725, 1942.
2. Vail, D.: Symposium cataract extraction: Intracapsular extraction: mechanics, technique, variations. Tr. Am. Acad. Ophth., **58**:367-370 (May-June) 1954.
3. ———: The zonule of Zinn and ligament of Wieger (Doyne Memorial Lecture, 1957). Tr. Ophth. Soc. U. Kingdom, **77**:441-449, 1957.
4. ———: Zonule membrane and cataract extraction. Am. J. Ophth., **48**:405, 1952.
5. Reese, A., and Wadsworth, J.: The adhesion of the lens capsule to the hyaloid membrane and its relation to intracapsular extraction. Tr. Am. Ophth. Soc., **54**:709-728, 1956.
6. Barraquer, J.: Enzymatic zonulysis: Contribution to surgery of the lens. 65th Cong. French Ophth. Soc., Paris, May, 1958.

REFLECTING MIRROR*

For the Schepens binocular ophthalmoscope

Enrique Malbran, M.D.
Buenos Aires, Argentina

The indirect binocular ophthalmoscopy obtained through the ophthalmoscope invented by Schepens is one of the greatest advances made during recent years in ophthalmologic practice. I shall not comment here on the important advantages of this ingenious method; I only wish to communicate the promising possibilities which are offered by a new apparatus which is called a "reflecting mirror."

Every ophthalmologist who has used the Schepens indirect binocular ophthalmoscope in a sufficient number of cases to be able to adapt himself to its handling knows the initial difficulties in learning how to use it, as well as the impossibility of showing to those who are not familiar with it, or are incredulous, the enormous advantages it brings for a better examination of the topography of the fundus, especially for retinal detachment diagnosis and surgery.

Recently, the firm of Keeler in England announced the creation of a "reflecting plate" for a second observer, adapted to the indirect binocular ophthalmoscope which they manufacture, the Fison model with

* This instrument is manufactured by the Sais Laboratories, Viamonte 2182, Buenos Aires, Argentina.

which we are already familiar.

On not finding any description of this new system in the ophthalmologic literature, I decided to construct, with the invaluable collaboration of Mr. Juan Sais (Sais Laboratories), an apparatus with which the same possibilities could be obtained. After a short period of necessary tests, we were able to make the new accessory for the ophthalmoscope manufactured by the American Optical Company.

The apparatus consists of a dark plastic adapter which may be added at will to the original ophthalmoscope and a mirror, 20 by 40 mm. in size, made of white Kraun lenses with a one-way vision, placed at an inclination of 45 degrees to the principal line of observation (figs. 1 and 2). This mirror absorbs 60 percent of sunlight and, when actually in use, transmits 40 percent of the beam to the principal observer and reflects 60 percent to the second observer, placed laterally at a right angle to the former. The picture which this second observer receives is very clear. It is inverted vertically but maintains the normal directions horizontally. That is to say that, in contrast to what the main observer sees, the picture in the mirror shows the lower parts of the fundus in the upper part of the mirror and vice versa, while what is to the right or left of the observer in the fundus remains in the same position in the mirror. The decrease in luminosity caused by the absorbing faculty of the mirror does not create observation difficulties because the illumination power of the Schepens ophthalmoscope is more than sufficient to overcome these inconveniences.

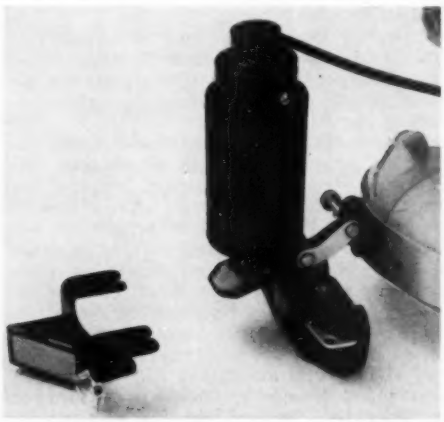


Fig. 1 (Malbran). The reflecting mirror.

Fig. 2 (Malbran). Apparatus assembled.

It is unnecessary to stress the innumerable advantages that this system offers for teaching, consultations with other colleagues, observation for assistants during the operation, and so forth.

A transparent plastic arm has also been added which enables one to adapt a Minox camera with which it is hoped to obtain photographs of the fundus and the results of which will be published together with our present tests on the filming of the fundus. I believe that this apparatus may be one more way of promulgating the advantages of indirect binocular ophthalmoscopy.

In our country, Dr. Escariz has recently made known the adaptation of the "Wesely relascope" for ophthalmoscopy (Arch. Oftal. Buenos Aires, **33**: 90–95 [June]

1959). This instrument has two lateral windows for observation which are used for the same purpose as the reflecting mirror just described.

Parera 94.

MALIGNANT MELANOMA OF CHOROID

Report of a case discovered after evisceration

Byron Smith, M.D.
and
David B. Soll, M.D.
New York

The purpose of this report is to record a case in which the diagnosis of malignant melanoma was established by histologic study of the contents of the eviscerated globe.

Case report

N. R., a Caucasian man, aged 64 years, noticed the gradual onset of diminished vision of the left eye in April, 1958. One month later, he was advised by an ophthalmologist to use drops in the left eye for the treatment of glaucoma. In spite of the regular use of the prescribed medication, however, the visual acuity of the left eye continued to decrease and the eye became congested and painful. The patient was first seen by us on June 1, 1958.

The vision in the right eye was 20/70, correctible to 20/20. The right eye exhibited no internal or external abnormalities, except for a few small, pigmented areas on the iris. The patient advised us that these spots had not changed in size, shape, or color. The visual field, gonioscopy, and tension of the right eye were normal.

The cornea of the left eye was steamy in appearance. The conjunctiva and episcleral tissues were congested. The left pupil was partially dilated and fixed. The iris vessels were dilated. Numerous keratic precipitates were scattered over the lower half of the corneal endothelium. Density and edema of the cornea prevented our determining whether there were any cells in the anterior chamber. The anterior chamber was so shallow that gonioscopy was nonrevealing. The lens was edematous and opaque. The ocular tension was 60 mm. Hg (Schiøtz). Anterior transillumination failed to reveal any variation in density.

A diagnosis of absolute glaucoma of unknown cause was made and the patient was admitted for treatment and observation. Physical examination, laboratory studies and a series of X-ray studies provided no additional diagnostic information. Radioactive-phosphorus studies were not carried out at this time. Antiglaucoma medication failed to normalize the ocular tension or eradicate the pain.

In view of the failure of medical treatment and in consideration of statistical evidence that four to 11 percent of blind eyes with opaque media contain malignant melanomas, histologic analysis of the ocular contents was advised.

Under general anesthesia on June 4, 1958, an incision was made through the conjunctiva and sclera, parallel to the equator of the globe in the upper nasal quadrant. A long cyclodialysis spatula was inserted to free the uveal tract completely from its scleral attachments. The incision was then extended parallel to the equator from the 3-o'clock to 9-o'clock positions, anterior to the insertion of the rectus muscles. The uveal tract and its contents were removed in one piece and sent to the laboratory for immediate study. After thorough curettage of the internal surface of the sclera, an 18-mm. plastic sphere was inserted. The sclera was closed with a continuous suture of 4-0 chromic catgut.

Twenty-four hours later the laboratory reported that the globe contents exhibited a dense, dark, firm mass histologically characteristic of malignant melanoma. The tumor was of the mixed-cell type, the predominant cells being spindle B and epithelioid cells, (figs. 1 and 2).

Forty-eight hours after evisceration, enucleation of the scleral shell was performed under general anesthesia. The conjunctiva, including the wound, was removed together with the sclera. No implant was used because it was felt that a more accurate postoperative follow-up would be possible in the absence of a surgically placed foreign body. Tenon's capsule was closed with 4-0 chromic catgut sutures. The conjunctiva was closed with 6-0 chromic catgut sutures. The postoperative course was uneventful. The patient was discharged from the hospital on the seventh postoperative day.

Histologic study of the optic nerve and Tenon's capsule showed no evidence of neoplastic disease. The scleral shell showed no microscopic evidence of malignant melanoma in the sections examined (fig. 3).

Three weeks after surgery, an artificial eye was fitted to the socket. Repeated examinations have disclosed no evidence of recurrent disease. Radioactive-phosphorus (P^{32}) uptake studies done on November 5, 1958, showed 24 percent the first hour, 27.3 percent in 24 hours, and 28.2 percent in 48 hours. The series of X-ray films taken on the same date revealed no neoplastic growth. The laboratory considered the report of the radioactive-phosphorus uptake studies essentially negative. A second radioactive phosphorus study in July, 1959, was also reported as negative for the superficial sites studied. Melanin tests of the urine taken during November, 1958, and July, 1959, were negative.

The patient was last seen on July 28, 1959, and at that time there was no evidence of recurrence (fig. 4).

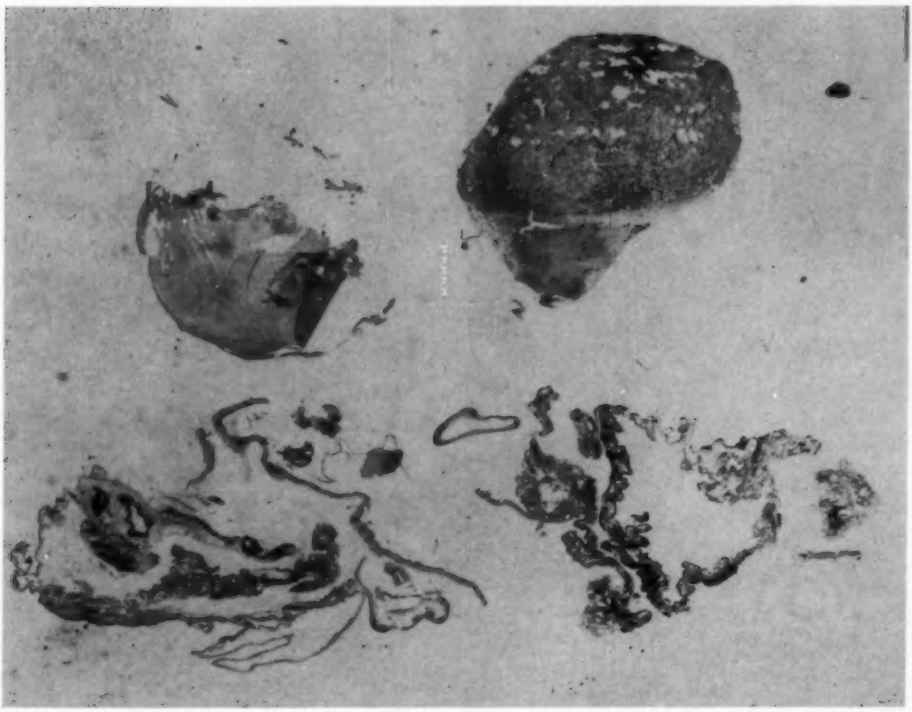


Fig. 1 (Smith and Soll). Section of the globe contents. The tumor mass is shown in the upper right corner of the photograph.

Discussion

Wilder and Paul reported a statistical study of longevity following enucleation for malignant melanoma. Eighty percent of the patients died within five years. Dunphy reported an over-all mortality of 48 percent within five years following enucleation for malignant melanoma. Westerved, Blandon and Zeeman conclude from their studies that the prognosis of malignant melanoma of the choroid in individuals beyond the age of 60 years is so poor that enucleation is of questionable value.

In a series of 210 cases studied by Wilder and Paul, it was concluded that the prognosis in a malignant melanoma exceeding 1,300 cu. mm. in size is more grave than it is in tumors of a smaller volume. The prognosis in malignant melanomas of the spindle-cell type is better than it is in tumors exhibiting a predominance of epithelioid-type cells.

Reese has stated that cases showing extrascleral extension prior to enucleation rarely develop orbital recurrence. His opinion is in accordance with others who believe that malignant melanoma cells gain entry to the circulation at an early stage of the disease.

Metastatic growths are dependent upon the ability of the cells to undergo independent growth. The character of the cell is the determining factor, rather than the mere presence of the tumor cells in blood or lymphatic fluids. Metastatic growth or a malignant melanoma has been reported to occur as late as 36 years following enucleation. Newton reported a case in which local recurrence occurred 14 years following enucleation.

The prognosis in this case, one year after

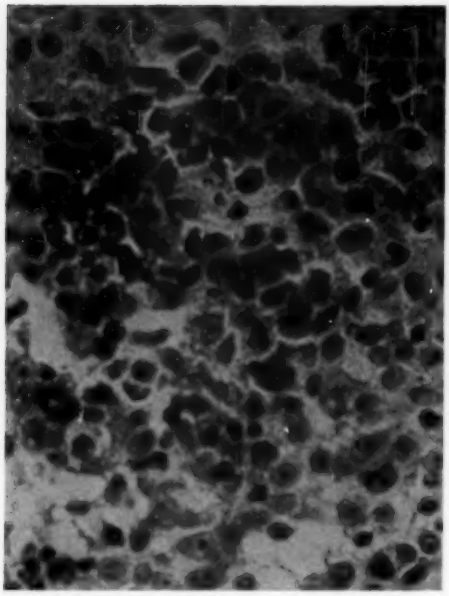


Fig. 2 (Smith and Soll). High-power view of the cellular structure of the tumor (×440).

surgery, appears optimistic, if one considers the present physical findings only but the tumor volume of more than 1300 cu. mm. and

Fig. 3 (Smith and Soll). Section of the excised scleral shell, showing the evisceration wound above. No tumor tissue was observed in the scleral sections.

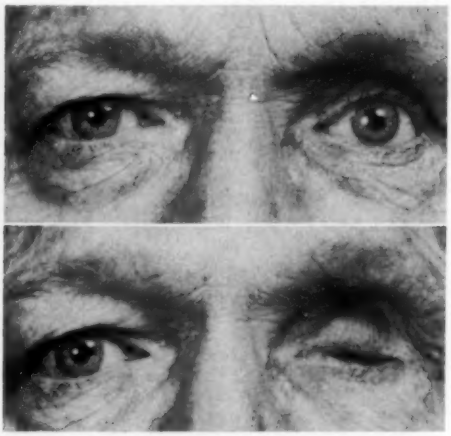


Fig. 4 (Smith and Soll). Prosthesis in the left socket after removal of the sclera. The lower photograph shows the exterior without the prosthesis in the socket.

the cell types present reduce the chances of a favorable outcome. The influence of surgery on the patient's prognosis is more dependent upon the character of the tumor than it is upon the surgery itself.

It is our hope that this case report will stimulate surgeons to request early examination of the contents of an eviscerated globe. The absence of tumor in the sections of sclera and optic nerve which were studied brings forth the question of the possibility of complete removal of malignant melanoma of the choroid by evisceration. In our opinion, the relative infrequent occurrence of malignant melanoma of the choroid and the questionable value of enucleation should encourage enthusiasm in a surgeon who prefers to do an evisceration instead of an enucleation in the apparently uncomplicated case.

In our experience, the most satisfactory means of acquiring the optimum cosmetic result is preservation of the cornea, evisceration, and intrascleral implantation of a sphere.

722 Park Avenue (21).

References

1. Makley, T. A., and Teed, R. W.: Unsuspected intraocular malignant melanoma. Arch. Ophth., **60**:475, 1958.
2. Wilder, H. C., and Paul, E. V.: Malignant melanoma of the choroid and ciliary body: A study of 2,535 cases. Military Surg., **109**:370, 1951.
3. Newton, F. H.: Local recurrence of melanoma of choroid 13 years after enucleation. Am. J. Ophth., **21**:668, 1938.
4. Rendahl, I.: Does exenteratio orbitae improve the prognosis of orbital tumors? Acta Ophth., **32**:432, 1954.
5. Chisholm, J. F.: A long-term follow-up on malignant melanoma of the choroid based on the Terry and Johns series. Am. J. Ophth., **36**:61, 1953.
6. Dunphy, E. B.: Management of intraocular malignancy. Am. J. Ophth., **44**:313, 1957.
7. Flocks, M., Gerende, J., and Zimmerman, L.: The size and shape of malignant melanomas of the choroid and ciliary body in relation to prognosis and histological characteristics. Tr. Am. Acad. Ophth., **59**:740, 1955.
8. Reese, A.: Quoted by Saunders, T. E.: Intraocular biopsy: An evaluation. Tr. Am. Ophth. Soc., **50**: 375, 1952.
9. Westover-Brandon, E. R., and Zeeman, W. P. C.: The prognosis of melanoblastoma of the choroid. Ophthalmologica, **134**:20, 1957.
10. Dunphy, E. B., Forrest, A. W., Leopold, I. H., Reese, A. B., and Zimmerman, L. E.: The diagnosis and management of intraocular melanoma. Tr. Am. Acad. Ophth., **62**:517, 1958.

SPHEROPHAKIA*

Y. Dayal, M.B., and K. S. Mehra, M.B.
Aligarh, India

Spherophakia, also known as microphakia, is a bilateral condition wherein the lens is small and at the same time spherical in shape (Guad, 1931). As a simple anomaly it is very rare. It may be associated with other congenital anomalies, such as ectopia lentis, persistent vascular sheath, corectopia, coloboma of uveal tissues, and aniridia; however, it is most common in association with ectopia lentis (Duke-Elder, 1937). The deformity is thought to be due to an aberration in the development of the whole lens system associated with the maldevelopment of the zonule.

Case report

An 18-year-old woman (fig. 1) complained of intermittent attacks of pain and headaches of several months' duration, with loss of vision for the last one month. She had had occasional fainting attacks since an early age and felt weak over her entire body. Since early infancy she had difficulty in seeing distant objects and had to bring near objects very close to her eyes. About five months ago she had noticed something in each eye which came forward and obstructed her vision but could be made to disappear on lying down.

Examination revealed prominence of both eyes with megalocornea and slight ciliary staphyloma. The corneas were hazy and edematous with opacities at places. The anterior chambers were slightly deep and each eye showed iridodonesis. The pupils were semidilated, inactive and were occupied in part by the lens.

Slitlamp examination revealed soft milky cataract, spherophakia, and microphakia. The position of the lenses changed with change in posture. Remnants of zonular fibers were seen floating in the pupillary area. There was also evidence of fluid vitreous in the anterior chambers. The fundus could not be seen.

Vision was reduced to hand movements close to the face in each eye. The intraocular pressure was 52 mm. Hg (Schiøtz), R.E., and 44 mm. Hg, L.E.

The systemic examination revealed no abnormality. Both the lenses were extracted intracapsularly (erisophake delivery) and a complete iridectomy was made without vitreous loss. The lenses were found to be 5.8 mm. diameter, O.U.

Four weeks later the visual acuity was corrected to: R.E., +9.0D. sph. ⊃+2.0D. cyl. ax. 150° = 3/60; L.E., +10D. sph. ⊃ +1.0D. cyl. ax. 180° = 4/60. The intraocular pressure was 25 mm. Hg (Schiøtz), R.E., and 23 mm. Hg, L.E. Media were hazy and the ophthalmoscopic examination dis-

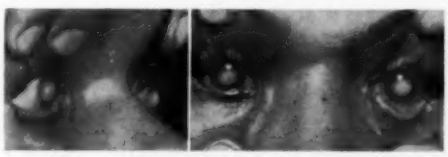


Fig. 1 (Dayal and Mehra). Appearance of patient.

* From the Gandhi Eye Hospital.

closed a glaucomatous cup in either eye. In addition a grayish strand surrounded by white tissue (glial and connective tissue) was seen arising from the optic disc, suggestive of a persistent hyaloid artery in either eye.

Discussion

The cause of spherophakia still remains speculative. The condition is supposed to be due to a congenital weakness of the zonule. There is an abnormal length and a partial tear of the zonular fibers. The traction of the zonular fibers on the crystalline lens, necessary for its normal development, is markedly diminished by this zonular deficiency. The lens remains in its primitive state, possibly in a spherical form and increases only a little in later development.

The cause of the maldevelopment of the zonules is unknown. It has been suggested that it may be a result of intrauterine inflammation (Leoz, 1922). Such theories postulate an ectodermal origin (Vogt, 1931; Franceschetti, 1932; Weill, 1932). In many cases like the one reported here, it may be associated with other deformities, such as persistent mesoblastic bands representing remnants of the vascular sheath of the lens, coloboma of the iris, ciliary body or the choroid, corectopia, or a spherophakia brachymorphia syndrome. This tempts us to classify the condition among the congenital systemic affections of the mesenchymal tissue.

The condition may be hereditary, being transmitted as a recessive characteristic in most of the cases but as a dominant type in a few.

Luxation of the lenses probably develops as a result of relatively minor trauma to the weakened zonule.

The hypertension is of the pupillary block type. But in cases where luxation has occurred, other factors, such as irritation of the ciliary body and blockage of the angle, may play an important role. Although the anatomic defects are congenital, the enlargement of the eyeball is not generally observed until several months after birth. In milder cases, drainage may remain adequate, often with little distention until years later when a hypertensive crisis occurs. In the case reviewed here, the distention probably occurred in early childhood, resulting in enlargement of the eyeball and a picture simulating buphthalmos.

Gandhi Eye Hospital.

References

1. Duke-Elder, S.: Textbook of Ophthalmology. London, Kimpton, 1937, v. 2, pp. 1348, 1350.
2. ———: Textbook of Ophthalmology. London, Kimpton, 1940, v. 3, p. 3307.
3. Jacoles: Am. J. Ophth., **20**:1042, 1937.
4. Mann, I.: Developmental Abnormalities of the Eye. London, Brit. M. A., 1957, ed. 2, p. 306.
5. Nirankari, M. S., and Mudgal, M. C.: Microphakia. Brit. J. Ophth., **43**:314, 1959.
6. Rosenthal, J. W., and Kloepfer, H. W.: The spherophakia-brachymorphia syndrome. A.M.A. Arch. Ophth., **55**:28, 1956.
7. Shapira, T. M.: Micro- and spherophakia with glaucoma. Am. J. Ophth., **17**:726-735 (Aug.) 1934.

STRATIFIED SQUAMOUS IRIS CYST

Unsuccessfully treated by repeated electrolysis

Noel T. Simmonds, M.D.
Alexandria, Louisiana

E. J. L., a white youth, aged 19 years, had bilateral congenital cataracts. Extracapsular cataract extraction with peripheral iridectomy right eye was done on June 14, 1955. Convalescence was uneventful. Ziegler capsulotomy was done on June 26, 1956. On September 4, 1956, he was found to have a small cyst of the iris at the 6-o'clock position.

On October 23, 1956, the cyst was treated by electrolysis, as described by Kennedy.* A Ziegler knife-needle puncture was made into the anterior

* Kennedy, P. J.: Treatment of cysts of the iris with electrolysis. A.M.A. Arch. Ophth., 55: 522 (Apr.) 1956.

chamber following which the electrolysis needle was inserted into the cyst which was soon filled with the usual foamy white mixture of hydrogen bubbles and protein acted upon by ions of sodium and potassium, and so forth. The needle was slowly withdrawn as the cyst collapsed and when the bubbles ruptured through into the anterior chamber the operation was discontinued.

On November 14, 1956, the cyst was found to be recurring. On November 19th it was again treated with electrolysis. On December 17th the cyst was again found to be recurring. The patient did not want to do anything about it before Christmas so it was deferred until January. On January 15, 1957, the cyst was again treated with electrolysis and at the same time my assistant made a keratome incision on the temporal side and irrigated the hydrogen bubbles and so forth out of the anterior chamber. In this way, it was possible to continue the electrolysis much longer than I would have dared otherwise. Even so, there was considerable edema of the lower half of the cornea which, however, cleared after about two weeks time. On February 20, 1957, approximately five weeks later, tension was found to be 48 mm. Hg (Schiøtz) in this eye. Pilocarpine and Diamox were used, reducing the tension to normal. On May 28, 1957, the last time I saw the patient before leaving on a two and a half months trip to Africa, there was still no evidence of the cyst recurring.

On August 21, 1957, shortly after I returned, he was again examined and the cyst found to have recurred. The cyst was about 3.0 mm. vertically by 1.5 mm. horizontally. With the corneal microscope cellular material could be seen floating in the cyst. Surgical excision was recommended, so on September 17, 1957, a preliminary Ziegler knife-needle puncture was made at the 6-o'clock position into the cyst which was in contact with the limbus at this point. This was done to empty the cyst extraocularly and evacuate the floating cellular elements to prevent seeding the anterior chamber with them in case the cyst ruptured, which it would probably have done if grasped when it was tense.

A scratch incision was then made at the limbus at the 6-o'clock position and enlarged with scissors, following which an iridectomy, including the cyst, was done. The incision was closed with 6-0 chromic catgut. There was no evidence of recurrence and the tension was normal without medication when the patient was last seen March 21, 1960. Dr. J. B. Maxwell, pathologist, found stratified squamous epithelium lining the cyst (figs. 1 and 2).

Fig. 1 (Simmonds). Low-power view of stratified squamous epithelium of iris cyst.

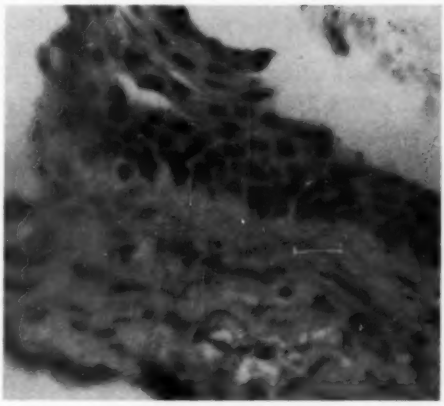


Fig. 2 (Simmonds). High-power view of stratified squamous epithelium.

Comment

In any treatment by electrolysis the cathode or negative pole is used as the active electrode. Positively charged hydrogen, potassium, and sodium ions are attracted to this electrode. Destruction of tissue by this method is essentially one of chemical destruction by the alkaline sodium and potassium ions and not by any direct destructive action of the electric current itself. Therefore, using a stronger current would not seem to be of any value.

The important thing it seems is to use it long enough to fill the cyst with a mixture of hydrogen bubbles and the caustic sodium and potassium ions and to apply the electrode to the iris as well as possible, remembering that the lens is immediately posterior to it.

After looking at the cyst under a microscope and seeing its numerous layers of cells one wonders whether or not it is possible to destroy the basal cell layer with this small amount of alkaline cauterization, in view of the fact that the electrode is not in contact with the cyst wall and therefore the alkaline cauterizing ions are much more diluted than

in epilation, and so forth, where the electrode is in direct contact with the hair follicle. Also, with the patient prone, the caustic products float away from the iris, from which the cyst actually grows.

Electrolysis is an excellent procedure and I feel sure that, in cases of simple cysts of the iris lined with endothelium, it is a very effective operation. It should be tried in all cysts, as it certainly shrinks them and does very little damage to the eye provided one is careful to have the patient lie on one side to prevent damage to the center of the posterior surface of the cornea by caustic electrolytic products floating up against it.

The reason for repeated attempts to destroy this cyst with electrolysis was to preserve as much iris as possible since the patient had a postoperative coloboma above due to the cataract extraction. However, the additional coloboma below has not caused any discomfort.

SUMMARY

A case of repeated failure to destroy a stratified squamous cyst of the iris by electrolysis is reported.

1300 Jackson Street.

THE T ILLUSION

F. H. VERHOEFF, M.D.
Brookline, Massachusetts

This illusion consists of three features. The first is that if two lines equal in length and breadth are drawn in the form of a T (fig. 1) upon a flat surface, the top, or divided line, appears much the shorter. This is remarkable enough, but the two other features are more so. The second is that no matter to what extent the T is rotated from up to down or from right to left, the divided line still appears much the shorter. The third feature, better seen binocularly, is that when the T is tilted forward or backward in any direction, even to an extent that in each eye makes the retinal image of the divided line much the longer of the two images, this line continues to appear the shorter. The illusion remains substantially the same when instead of lines three dots are used for demarcation.

Fig. 1 (Verhoeff). The T illusion.

Simple, conspicuous, and surprising, as this illusion is, I cannot find it has previously been described in a scientific publication. Its explanation is not at once evident but I feel sure that it depends upon monocular perspective and does not have a physical basis such as that of the Kundt illusion. I also feel sure that full explanation of all of its features will reveal facts highly important to the understanding of visual perception in general.

61 Monmouth Street (46).

SOCIETY PROCEEDINGS

EDITED BY DONALD J. LYLE, M.D.

YALE POSTGRADUATE SERIES

October 9, 1959

R. M. FASANELLA, M.D., *presiding*

ALPHA CHYMOTRYPSIN

DR. RICHARD TROUTMAN summarized his experiences with the use of alpha chymotrypsin, using double blind studies at the State University of New York. He showed films including his present technique of cataract extraction with alpha chymotrypsin and his modified motor-driven erisophake. The second film showed problems encountered in a cataract extraction in a child using alpha chymotrypsin and a third film showed Joaquin Barraquer's extraction of a cataract utilizing alpha chymotrypsin.

DR. FASANELLA read the following letter from Joaquin Barraquer dated September 13th:

"During the last months I have come to the conclusion that one or two minutes are definitely enough to obtain zonulysis in adults. Therefore, I irrigate the posterior chamber with alpha chymotrypsin after I have made the iridectomy and placed the sutures; immediately afterwards I wash the incision with saline solution or balanced salt solution ('Chibret') and a minute later I irrigate the anterior chamber with the same solution to wash out the chymotrypsin.

"One may have to wait a bit longer in younger individuals, but I found that a very short time of action is necessary to obtain zonulysis or at least a weakening of the zonule that permits easy extraction.

"With regard to the use of the enzyme in children, I have also tried the method suggested by Dr. Kaplin, but without success. As you know, I had a lot of trouble with my operations on children in September, 1958. Later, I reduced the time of action and again got good results, just as in my first series.

"In my opinion, the following points are essential: limbus-based flap; incision ab externo, coagulating well the slight hemorrhage in order to avoid blood entering the anterior chamber; medium-size peripheral iridectomy; the pupil must not be dilated in order to stop easily the vitreous humor; preliminary suture; irrigation with alpha chymotrypsin (1/5,000) and two minutes later irrigation of the anterior chamber in order to remove any remainder of the enzyme; the suction cup is applied with a vacuum of 40 or more and after some rotating movement, tumbling to separate the adhesion between lens and vitreous through massage with the posterior face of the cornea; tie the sutures and, if necessary, get the pupil round with a spatula; fill the anterior chamber more or less with saline solution, not with air.

"In spite of observing all these points, the operation remains difficult and a lot of experience will be needed until this problem can be resolved. Personally, as a routine, I am doing extracapsulars in children."

DR. ERNEST ROSENTHAL commented on experimental work using delta chymotrypsin.

DR. LEONARD FLOM commented on his experience with the use of alpha chymotrypsin in a traumatic cataract and pointed out that no further injury was encountered.

October 23, 1959

DR. GEORGE D. PAPPAS spoke on "Electron microscopy of the ciliary body and its relation to aqueous secretion" which was published in full in the *A. M. A. Archives of Ophthalmology*, December, 1959.

DR. COULOMBRE called attention to difficulties encountered in this work.

DR. LOVEKIN called attention to the behavior of the thorium dioxide and sodium fluorescemate, remarking that this might lead to a new theory on the etiology of glaucoma.

Stephen Troubalos,
Recording Secretary.

COLLEGE OF PHYSICIANS OF PHILADELPHIA

Section on Ophthalmology

November 19, 1959

Harold G. Scheie, M.D., *Chairman*

Pigmented tumors of optic nervehead

Dr. Lorenz E. Zimmerman, Washington, D.C., delivered the 22nd annual deSchweinitz lecture and presented evidence that there is a distinctive locally invasive but probably nonmalignant primary melanotic tumor of the optic disc, that this tumor probably arises from normal uveal melanocytes which may be found in the nervehead of many animals and deeply pigmented humans, and that it may not be truly neoplastic but rather hemartomatous or progonomatous. From a practical standpoint the tumor is important because it has so often been mistaken for a malignant melanoma of the uvea that has invaded the nervehead.

* * *

December 17, 1959

Sturge-Weber syndrome

Dr. Richard M. Lubowitz (by invitation) reported two cases of the Sturge-Weber syndrome with pathologic examination of the involved eyes.

The first case, in a 53-year-old white woman, had a history of a congenital facial hemangioma on the left and a divergent left eye since childhood. She was seen in clinic in 1935 and found to have a divergent left eye and vision limited to light perception. The tension was elevated, there was a glaucomatous cupping and optic atrophy. No fundus lesion was reported. In 1958 the eye became painful, the tension was high and vision was nil, so the eye was removed.

Microscopic examination revealed peripheral anterior synechia, atrophy of the ganglion cell and nerve fiber layers of the retina, cupping of the disc and optic atrophy. There was a diffuse hemangioma of the choroid, causing very little change in its thickness.

The second case, in a 57-year-old white man, had a history of a congenital nevus flammeus of the left side of his face and glaucoma in the left eye for at least 20 years. This was a shrunken, bony hard globe and microscopic examination demonstrated a thickened, scarred cornea, total anterior synechia with absent anterior chamber, cataractous lens, and a retrolental cyclitic membrane.

The retina was detached, and there was extensive bone formation between the retina and choroid which contained a large cavernous hemangioma.

Carbonic anhydrase in the young eye

Dr. Jubran G. Mamo (by invitation) said that in the rabbit embryo carbonic anhydrase appears early and in high concentrations in the blood, the liver, and the eye. The carbonic anhydrase activity of the fetal eye is predominantly due to the lens which is large in size compared to the other ocular structures.

Previous reports tend to deny any important function of this enzyme in the adult rabbit and human lens. It seems very likely that carbonic anhydrase plays a role related to the development of the lens.

Heparin in diabetic retinopathy

Dr. John K. Finley and Dr. Harry S. Weaver administered 1,500 international crude units of heparin four times daily through the sublingual route to 10 patients with diabetic retinopathy for a six-month period. Reduction in the amount of fasting serum chylomicrons concomitant with partial clearing of the characteristic diabetic retinal lesions was noted. The authors consider their results favorable. However, they believe a longer therapeutic period necessary for complete evaluation of the therapy.

William E. Krewson, 3rd,
Clerk.

AMERICAN JOURNAL OF OPHTHALMOLOGY

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Address original papers, other scientific communications including correspondence, also books for review to *Dr. Derrick Vail, 700 North Michigan Avenue, Chicago 11, Illinois;* Society Proceedings to *Mrs. Katherine F. Chalkley, Lake Geneva, Wisconsin.* Manuscripts should be *original copies,* typed in *double space,* with wide margins.

Exchange copies of the medical journals should be sent to *Dr. F. Herbert Haessler, 561 North 15th Street, Milwaukee 3, Wisconsin.*

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Change of address notice should be received not later than the 10th of the month prior to the issue for which the change is to go into effect. Both old and new addresses should be given.

Author's proofs should be corrected and returned within forty-eight hours to the *Manuscript Editor, Mrs. Katherine F. Chalkley, Lake Geneva, Wisconsin.* Fifty reprints of each article will be supplied to the author without charge. Additional reprints may be obtained from the printer, the George Banta Company, Inc., Curtis Reed Plaza, Menasha, Wisconsin, if ordered at the time proofs are returned. But reprints to contain colored plates must be ordered when the article is accepted.

FRANCIS HEED ADLER, EDITOR

It is an honor and pleasure indeed to announce to our readers that Francis Heed Adler, M.D., of Philadelphia, has consented to accept the appointment of consulting editor to THE JOURNAL.

Dr. Adler served as the chief editor of the *A.M.A. Archives of Ophthalmology* from 1949 to 1960 with the greatest distinction. During this time he successfully guided its destiny and influence in an ever-increasing curve upward, not only in regard to its circulation but especially in the quality and standards of the scientific contributions to our specialty, that he scrupulously selected for publication.

He devoted a large amount of time and effort to this influential position, bringing to his

task a superb knowledge of all of the clinical aspects of ophthalmology; a training in and a deep knowledge of laboratory technique; scientific integrity and superior judgment.

His versatility in all fields of ophthalmology are too well known to require details here. His talents and genius as a clinician, surgeon, editor, writer of textbooks, teacher and investigator in the clinic and the laboratory are widely recognized and appreciated.

The trustees of the American Medical Association, in their infinite wisdom, last year passed a rule requiring the editor of each of its special journals to resign after 10 years of service, no matter what. So, although Dr. Adler had expected to serve for a few years more according to the original agreement, he was summarily made to resign. It is a great loss to the *Archives,* but a most welcome gain to THE AMERICAN JOURNAL OF OPHTHALMOLOGY. As they say in sporting circles, we have hit the jack-pot.

It is good to know that the superb editorial skills of Francis H. Adler will not be lost to ophthalmic literature. As consulting editor to this great JOURNAL, known and acclaimed throughout the world, his remarkable talents will be available to us all for the betterment of THE JOURNAL. His mature and experienced advice and counsel will be sought on occasion of difficult decision. His skill as a writer will have the utmost freedom in the development of whatever editorials he may care to contribute. We go on from strength to strength.

Derrick Vail.

THE MIAMI BEACH MEETINGS, 1960

Miami Beach proved to be an interesting and unusual meeting place for the annual sessions of the American Medical Association and Association for Research in Ophthalmology June 13-17, 1960. The rococo of the Florida Gold Coast, the blue Atlantic, the easily available resort facilities, and the contrast between air-conditioned interiors and the humid outdoors made for a memorable meeting. Air travel to Miami was complicated by a walk-out of air line pilots so that many arrived hours late, tired and dishevelled after long frustrating hours spent in distant airports as "standbys" before unclaimed seats materialized. However, the scientific material presented and hospitality extended were outstanding and probably everyone found the meetings well worth the discomforts of transportation.

The program of the Section on Ophthalmology under the chairmanship of Harold G. Scheie was an outstanding variety of diagnostic and surgical ophthalmology. The final day was devoted to ocular surgery and the meeting room was crowded from beginning to end to hear the invited foreign guests: Barraquer of Barcelona, Strampelli of Rome, and Choyce of London, plus equally distinguished American ophthalmologists.

Scheie, in the chairman's address, described the use of goniopuncture in infantile glaucoma in which goniopuncture, combined with goniotomy, was successful in 76 percent of the eyes. Goniopuncture alone was effective in 52 percent and goniotomy alone in 62 percent of the cases. The combined procedure was unusually effective in various types of juvenile glaucoma and would seem to be the operation of choice in these desperate, distressing cases.

Barraquer showed dramatic motion pictures of lens extraction using alpha chymotrypsin and generally concurred in the recommendations of the Academy committee concerning its indications and contraindications. He uses an unusually full corneal incision, and a limbal-based flap when alpha chymotrypsin is used, irrigates the enzyme from the eye after the lens is dislocated, and constricts the pupil with 1:10,000 acetylcholine before inserting additional appositional sutures. The discussion which followed suggested that the use of alpha chymotrypsin is spurring a resurgence of the Smith extraction and that increasing numbers of surgeons are not grasping the lens with an instrument if the enzyme is used.

The demonstration of anterior chamber lenses by Benedetto Strampelli and D. Peter Choyce stimulated considerable interest, awe, and latent conservatism in many viewers. The skill and energy of these brilliant surgeons in developing the lenses, the painstaking technique required for insertion and their great clinical experience were most evident. One had the feeling, however, that ocular surgeons in this country, despite the material presented, are not yet psychologically ready to adopt the procedure as a routine.

In other papers Trygve Gundersen of Boston described the use of the thin conjunctival flap dissected from above, combined with peripheral lamellar keratectomy to relieve the pain of bullous keratopathy and in some instances to reverse the edematous process. James H. Allen of New Orleans comprehensively discussed the pathologic changes in the cornea in leprosy and presented an exhibit on the same topic, one that has been surprisingly neglected in the past. Contact lenses in aphakia was discussed by Robert C. Welsh of Miami and the acute complications of corneal lenses were presented by Richard K. Lansche and Robert Lee of Munich, Germany. It seemed evident that ophthalmologists are developing a much greater interest than before in the application, fitting and complications of contact lenses. This interest was reflected too in the action of the House of Delegates, sparked by energetic Ralph O. Rychener, in expressing grave concern over the indiscriminate use of the contact lens and in pointing out that the fitting of contact lenses is a proper medical function of a physician.

At the executive session the Knapp Medal for Distinguished Service to Ophthalmology was awarded in a moving tribute by the doyen of organized ophthalmology, Arthur J. Bedell, to Parker Heath for his contributions as professor of opthalmology at two medical schools, custodian of the Knapp fund, and as an ocular pathologist. The scientific medal of the Section was awarded to Frederick C. Cordes in recognition of his achievement in creating the outstanding department at the University of California and his contributions to the science, literature, and organization of ophthalmology.

The officers of the Section elected for 1961 are Banks Anderson of Durham, North Carolina, to succeed Harold G. Scheie as chairman, and Gordon M. Bruce of New York City as vice chairman to succeed Paul A. Chandler. Henry F. Allen continues as secretary. Ralph O. Rychener of Memphis, Tennessee, was reelected delegate of the Section to the House of Delegates and Frank W. Newell of Chicago, Illinois, representative to the Council on Scientific Exhibits.

Restriction of space limited the scientific exhibits in ophthalmology to 10 but four of these were winners of awards. The highest award of the American Medical Association, the Hektoen Gold Medal which is presented for exhibits of original investigation and judged on the basis of originality and excellence of presentation, was awarded to Hermann M. Burian, Gunter K. von Noorden, Lee Allen, and Ignacio V. Ponseti, State University of Iowa College of Medicine, Iowa City, for the exhibit on "Chamber angle anomalies in developmental glaucoma and in systemic mesodermal disorders." This exhibit also won the $250 prize of the Section for the best exhibit. Additionally, Mr. Lee Allen was awarded a certificate of merit for his work on the medical illustrations in this exhibit.

Other awards to the Section on Ophthalmology exhibits were: Certificate of Merit to Robert A. Schimek and Homer D. Kirgis, Ochsner Clinic and Tulane University School of Medicine, New Orleans, for the exhibit on "Ophthalmodynamometry: A diagnostic aid in cerebrovascular disease."

Certificate of Merit to Lorenz E. Zimmerman, Armed Forces Institute of Pathology, Washington, D.C., William F. Hughes, University of Illinois College of Medicine, Chicago, and Sam T. Jones, University of Oregon Medical School, Portland, Oregon, for the exhibit on "Clinicopathology study of the cornea."

Honorable Mention to DuPont Guerry, III, Walter J. Geeraets, and Wolfgang A.

Lieb, Medical College of Virginia and Titmus Research Laboratory, Richmond, Virginia, for the exhibit on "Anterior chamber lenses."

The Section prize of $250 for the best presentation of a paper was awarded to Joseph L. Dowling, Jr., of Providence, and Taylor R. Smith of Boston, for a "Study of pulseless disease." Injection of the retinal vascular tree with India ink in a well-documented case indicated multiple microaneurysms, irregular dilation of the veins, and apparent arteriovenous anastomoses.

Thirty papers presenting the usual wide spectrum of ophthalmic research topics were presented at the Association for Research meeting under the direction of James H. Allen, chairman of the Board of Trustees. Attendance at each of the sessions was unusually good and reflected the explosive expansion of ophthalmic research in recent years.

The demonstration of Becker and Forbes of St. Louis of an active intraocular transport system which removes organic anions in vivo and in vitro seemed likely to open an entirely new field of study of transport mechanism within the eye. Dowling of Cambridge, Massachusetts, presented data quantitating the electroretinogram with the concentration of visual pigment in vitamin-A deficient rats. The administration of vitamin-A acid prevented bodily changes of vitamin-A deficiency but did not prevent or cure night blindness due to deficiency. Thus it was possible to extend studies far beyond previous ones in which the systemic deterioration due to vitamin-A deficiency interfered with the retinal studies.

Sir Stewart Duke-Elder, recipient of the Proctor Medal, took as his theme "Gaudeamus igitur dum iuvenes summus" and with his sparkling, rhythmic speech reviewed scientific progress in ophthalmology during the past century. He asked particularly that scientists, "Replace present-day worship of technical 'know-how' by a more fundamental question of 'know-why'."

The Friedenwald Memorial Lecture was presented by Irving H. Leopold who discussed the anticholinesterases with his customary competence. Leopold has done some of the fundamental studies in bringing several of these compounds from the laboratory to clinical medicine and his lecture indicated that new inhibitors of cholinesterase and information concerning their mechanism of action will continue to develop.

Major changes were made in the administrative structure of the Association for Research at the business meeting. Dues were increased to $15.00 annually for regular members and $5.00 for educational members. Lorand V. Johnson, who has been secretary-treasurer of the group since 1955 and who stimulated many organizational changes and doubled membership, was succeeded by Monte G. Holland of New Orleans as secretary, Robert Moses of St. Louis as assistant secretary, and A. Ray Irvine of Los Angeles as treasurer. Bernard Becker of St. Louis was elected trustee. Honorary members elected were Miss Mildred Weisenfeld of the Fight-for-Sight, National Council to Combat Blindness, and Drs. Everett L. Goar and Francis Heed Adler.

Plans were presented to expand the midwinter meeting, since it is evident that there is a greater amount of ophthalmic research than can be presented at a single national meeting. The trustees hope that this midwinter meeting will be held annually in the home city of the chairman. Thus, the next midwinter meeting will be in Chairman James Allen's New Orleans at the Roosevelt Hotel, December 5, 6, and 7, 1960. Bernard Becker is program chairman. The happy union between the Section on Ophthalmology and the Association for Research is expected to continue and the annual meeting of the Association will be in conjunction with the American Medical Association annual meeting.

The next annual meeting of the American Medical Association will be in New York City June 26-30, 1961.

FRANK W. NEWELL.

A BOO BOO

Readers of the June number of *A.M.A. Archives of Ophthalmology* (**63**:907, 1960) must have been amazed and startled to see in an editorial by John H. Talbott, M.D., editor of the *Journal of the A.M.A.*, a statement that "the new *Archives* assumed all responsibilities of the three periodicals that published ophthalmic literature in America." Included in these was THE AMERICAN JOURNAL OF OPHTHALMOLOGY!

1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, twenty!

The following letter, dated June 29, 1960, was dispatched to Dr. Talbott. I think it is informative, and should help to correct this stupid error.

John H. Talbott, M.D.
Editor, Journal American Medical Association
534 North Dearborn Street
Chicago 11, Illinois

Dear Dr. Talbott,

In your editorial in the June number of the *A.M.A. Archives of Ophthalmology* (**63**:907, 1960) discussing the retirement (forced) of Francis Heed Adler as editor-in-chief of the *Archives* and the appointment of David C. Cogan to replace him, you make several serious mistakes. They are serious from the usual viewpoint that an editor of any publication must maintain scrupulous accuracy in any of his published statements, and from my own viewpoint as editor-in-chief of THE AMERICAN JOURNAL OF OPHTHALMOLOGY for 20 years.

You say, "The *Archives of Ophthalmology* was founded in the year 1928 with Arnold Knapp as chief editor." (You mean that in 1928 the A.M.A. "took over" the *Archives*). You go on to say that the new *Archives* assumed all responsibilities of the three periodicals that published ophthalmic literature in America (there were and are more than three being published), the *Archives of Ophthalmology* founded by Herman Knapp in 1869, the *American Journal of Ophthalmology* (sic) and the *Ophthalmic Yearbook* "(likewise sic!)." Incidentally, the title of the last should be *Ophthalmic Year Book*.

While I don't propose to do the necessary historical and literary research here, for you with all the high powered secretaries, aids, libraries, etc., at your beck and call, let me review briefly for you the history of the *Archives*, THE AMERICAN JOURNAL OF OPHTHALMOLOGY and the *Ophthalmic Year Book*.

Archives of Ophthalmology

The *Archives of Ophthalmology* began in 1869 under the title "*Archives of Ophthalmology and Otolaryngology*, edited and published simultaneously in English and German by Professor H. Knapp, M.D., in New York and Professor S. Moos, M.D., in Heidelberg. Published by William Wood and Co., New York."

"In 1879, Vol. VIII appeared as the *Archives of Ophthalmology*, edited in English and German by Dr. H. Knapp of New York and Dr. J. Hirschberg of Berlin. Published by G. P. Putnam's Sons, New York."

The *Archives* went on like this until the death of Herman Knapp in 1911 (April 30) (see obituary, *Archives of Ophthalmology*, **40**: 357, 1911), when Dr. Knapp's distinguished son, Arnold, assumed the editorship (with the collaboration of Ward Holden).

After the A.M.A. "took over" the *Archives* in 1928, Volume I of the new series appeared in 1929 (Arnold Knapp, Editor); with Volume 41, 1949, Dr. Adler became chief editor.

THE AMERICAN JOURNAL OF OPHTHALMOLOGY

In 1862, a German ophthalmologist named Julius Hornberger, M.D., settled in New York and established a small quarterly journal which he called *The American Journal of Ophthalmology*. With the sixth number in 1864, this journal folded up. Incidentally, the second number was dedicated to the Emperor Maximilian of Mexico.

In 1884, Adolph Alt of St. Louis began a new AMERICAN JOURNAL OF OPHTHALMOLOGY. It ran continuously until 1918 when Edward Jackson, M.D., of Denver, began what is called Series 3. It amalgamated the *Annals of Ophthalmology* (James Parker, M.D.) 1892-1918, and the *Ophthalmic Record* (G. S. Savage, M.D.) 1892-1918.

At no time did any of these volumes of THE AMERICAN JOURNAL OF OPHTHALMOLOGY come under the direction or responsibility, and certainly not the influence, of the American Medical Association.

The *"Ophthalmic Year Book*, a digest of the Literature of Ophthalmology with Index" was founded in 1903 by Edward Jackson, M.D. In 1904 George deSchweinitz, M.D., of Philadelphia, and later T. B. Schneiderman, collaborated with Dr. Jackson. In 1924, William H. Crisp, M. D., of Denver, assumed the responsibility of the *Year Book*. The last issue was published (by the Ophthalmic Publishing Company, the parent body of THE AMERICAN JOURNAL OF OPHTHALMOLOGY) in 1927.

At no time did the *Ophthalmic Year Book* come under the direction or responsibility and, again, certainly not the influence, of the American Medical Association.

I don't know whether to be angry or amused by your statements. It is flattering that you should claim THE AMERICAN JOURNAL OF OPHTHALMOLOGY as a responsibility of the A.M.A. because almost all ophthalmologists here and abroad think it to be the best ophthalmic journal in English in the world. I agree with this sentiment, so I am amused.

I am angry because THE AMERICAN JOURNAL OF OPHTHALMOLOGY has reached this peak of acclaim through hard work that was independent of any medical organization, without subsidy of any kind, and that you were ignorant of this important fact.

THE AMERICAN JOURNAL OF OPHTHALMOLOGY is free and independent. The directors, editor, and associate editors wear no man's collar or chain. We are responsible, and proudly so, for our own policies and actions. We are free of any control by the trustees of any medical or lay organization whatsoever, trustees who are able to dismiss one of the greatest editors in opthalmology most summarily.

I will appreciate it if you will publish this letter in the *Journal of the American Medical Association* and in the *A.M.A. Archives of Ophthalmology*.

Sincerely yours,
Derrick Vail, M.D.

"O hateful error, melancholy's child
Why dost thou show to the apt
thoughts of men
The things that are not?"
Julius Caesar, Act V, Sc. 3.

INTERNATIONAL COUNCIL OF OPHTHALMOLOGY

A meeting of the International Council of Ophthalmology took place at Athens on April 16, 1960.

Present: Duke-Elder (president), Berens (vice president), Hartmann (secretary), Streiff (treasurer), Bietti (International Organization against Trachoma), Franceschetti (Association for the Prevention of Blindness), François (European Society of Ophthalmology), Coppez (president of the last congress), Sen (president of the next congress), Arruga, Lyle, MacDonald, Müller, Paufique, and Weve.

The president reported the death of three late members of Council: Alvaro, Samuels, and Velter.

The following is a brief résumé of the more important matters of interest.

1. Dr. Jorge Valdéavellano of Lima, having been elected president of the Pan-American Association of Ophthalmology in place of Dr. Brittain Payne, has become an ex-officio member of the International Council.

2. The Bulgarian Society of Ophthalmology was accepted as an affiliated member of the Federation of Ophthalmological Societies.

3. The XIX International Congress of

Ophthalmology will be held in New Delhi from December 3 to 7, 1962. An opening reception will be given by the President of the Indian Republic. In view of the relatively small number of hotels in New Delhi, those proposing to attend the Congress are asked to register before January 1, 1962. The official agents for accommodation and travel are the American Express and two Indian agencies —Mercury and Trade Wings. The registration fee should be paid before January, 1962.

The two official discussions chosen for the Congress are:

a. Ocular lesions in tropical parasitoses, introduced by B. N. Bhaduri (Calcutta), Cyro de Rezende (Sao Paulo), A. Larmande (Algiers).

b. Corneal degenerations, introduced by G. Bietti (Rome), A. G. Leigh (London), A. E. Maumenee (Baltimore).

The following four symposia will occur: (a) The complications of cataract surgery; (b) Eales' disease; (c) Electron microscopy in ophthalmology; (d) Ophthalmological problems in aviation.

Free papers will be strictly limited to 50, and a committee consisting of Duke-Elder, H. K. Müller, and G. Bietti, has been formed to select them. Delegates to the Congress wishing to read a paper should send a summary in French and English before January 1, 1962, to Sir Stewart Duke-Elder, Institute of Ophthalmology, Judd Street, London, W.C. 1, England.

4. The next meeting of the council will be held at Oxford on Saturday, July 8, 1961, just before the meeting of the Oxford Congress.

Stewart Duke-Elder.

CORRESPONDENCE

Unmasking a deception

Editor,
American Journal of Ophthalmology:

In the June, 1960 issue of The American Journal of Ophthalmology, we noted the review by Dr. James E. Lebenson of the book *You and Your Eyes*, by Lawrence Lewisohn and hasten to write you in this regard.

For your information, previous to publication of *You and Your Eyes*, representatives of the author contacted the National Council to Combat Blindness, Inc., "the Fight For Sight," with the offer that Lawrence Lewisohn wished to contribute part of the proceeds from the sale of this book to this organization. In return for this, he requested the privilege of publicity announcing this fact.

After consultation with the chairman of our Scientific Advisory Committee, we told the representatives that we could not accept such proceeds, nor could the author or any of his representatives use the name of our organization in connection with the book. Despite this, we were informed by individuals in New York City and in Los Angeles, that public mention was made by Lawrence Lewisohn, stating that part of the proceeds of the book would benefit the Fight For Sight, the National Council to Combat Blindness, Inc. We immediately protested in writing to Lawrence Lewisohn's representatives and, in turn, received a letter of retraction.

We cannot, however, be entirely certain that the name of our organization was not again used in connection with *You and Your Eyes* and we wish to go on record, that the National Council to Combat Blindness, Inc., the Fight For Sight, in no way endorses this book, nor will it accept proceeds from its sale.

(Signed) Mildred Weisenfeld,
Executive Director,
New York.

A correction

Editor,
American Journal of Ophthalmology:

The "Atlases of Ophthalmoscopy: A bibliography, 1850-1960," by Thomas E. Keys, M.D., and C. Wilbur Rucker, M.D., published in The Journal, May, 1960 omitted two important facts regarding my atlases.

The 1929 *Atlas* consisted of actual photo-

graphic copies made from the original negatives. They were the first in the world. The Dimmer and Pillat illustrations were lithographic reproductions.

My 1946 *Clinical Ophthalmoscopy* was not even mentioned although it is the most widely used collection of fundus photographs. Practically every medical college uses them in class work and conferences.

(Signed) Arthur J. Bedell,
Albany, New York.

BOOK REVIEWS

THE ESSENTIALS OF PERIMETRY. By Howard Reed, M.B., F.R.C.S., etc. Foreword by Arnold Sorsby M.D. London, New York, Toronto, Oxford University Press, 1960. 182 pages, 167 illustrations, selected bibliography, index. Price. $10.50.

The author is in the Department of Ophthalmology, University of Manitoba. Sorsby points out in his foreword that the author was responsible for courses of lectures on the principles of perimetry delivered to students at Moorfields, preparing for the Diploma in Ophthalmology (D.O.). These lectures stressing basic pricinples are here presented in book form. The reader will agree with Sorsby who said that "these were good lectures," bearing out the old truth that it "takes a master to expound adequately the elements of a subject."

In view of the many excellent books and treatises on perimetry in English, French and German that are available in recent up-to-date editions, it can be questioned if there is room for another. I am sure that there is room for this one, for it is a welcome addition to our library.

The illustrations by Miss Nancy Joy, medical artist in the Department of Surgery, University of Manitoba, are most excellent and to the point.

The book is simply divided into three parts. Part I concerns the applied anatomy of the visual pathway; Part II, the visual field and its assessment; and Part III, field defects and their interpretation. The somewhat austere uncluttered but always lucid style of the author, generously supplemented with the excellent line drawings of Miss Joy, makes the subject quite clear and stimulating.

I think it is an excellent book to be in the hands of every student and resident in ophthalmology and neurosurgery, as well as in those of every clinician in these fields. In fact, it would not be surprising that even a nonmedical technician could understand the issues involved and would be immensely benefited by a close study of this book.

Derrick Vail.

FROM FISH TO PHILOSOPHER: THE STORY OF OUR INTERNAL ENVIRONMENT. By Homer W. Smith, Ph.D. Ciba edition, revised and enlarged, Summit, N.J., Ciba Pharmaceutical Products, 1959. Paperbound, 304 pages, 12 figures, bibliography, index. Price: Free on request.

Dr. Smith's revision of his very readable book, the first edition of which appeared in 1953, is among the notable contributions published to celebrate the centennial of Darwin's *Origin of Species*. The broad scope of this book fittingly supplements Duke-Elder's *The Eye in Evolution*. Claude Bernard referred to the tissue fluid as the internal environment—the true medium in which the body lives. The responsibility for maintaining its composition devolves on the kidneys. Should the kidneys fail, neither muscle, brain nor eyes could carry on.

Evolution is opportunistic in that every conceivable device gets tried. "It seems nearly impossible to think of a practical photoreceptor that has not appeared in one group of animals or another, ranging from the diffuse sensitivity of unspecialized cells to the elaboration of many different types of compound eyes, and to the simple eye of man. . . . It is natural selection that turns the randomness of natural variation into an organically useful plan."

Garstang (1894) first suggested the larval echinoderms as a likely source of vertebrate ancestry. The australopiths discovered in southern Africa, which are possibly a million years old, conform closely to the looked-for connecting link between the anthropoid-apes and the later hominids of the Pithecanthropus genus. Modern man emerged about 40,000 years ago. He is said to differ in having learned how to learn.

The profession is indebted to the Ciba Company for the publication of this stimulating monograph in a free paper-back edition, as with *The Rauwolfia Story* (THE JOURNAL, **39**: 257 [Feb. Pt. 1] 1955) and the Ciba Symposia.

James E. Lebensohn.

L'ANNÉE THÉRAPUETIQUE ET CLINIQUE EN OPHTALMOLOGIE. Edited by G. E. Jayle and A. DuBois-Poulsen. Marseille, Fuery-Lamy, 1959, Volume X, 335 pages, index. Price: $10.00.

This volume marks the 10th anniversary of the first appearance of this most useful series, and continues the subject of ocular surgery with which Volume IX was concerned. Chapters are devoted to anesthesia and its complications, postoperative ocular infections, decubitus, and failures and complications of various types of ocular surgery, written by well-known French experts. It contains much information of considerable note and French-reading ophthalmologists will find much in it of profit to themselves and their patients.

Volume XI will cover the subject of "Industrial ophthalmology."

Derrick Vail.

THE INFLUENCE OF THE ADRENAL CORTICOIDS ON THE INFLAMMATORY REACTION OF THE EYE. By Wilhelm Böke, M.D. Leipzig, Georg Thieme, 1960. 104 pages, 29 illustrations, bibliography. Price: DM 21.70.

After a discussion of the general physiologic and pathophysiologic effects of the corticoids on the eye, Böke concerns himself with the clinical application of cortisone and its derivatives; the indications for the use of steroids; and the results and failures of their use. With wise restraint he cautions against the overly enthusiastic and indiscriminate administration of these potent drugs. He is in favor of limiting this form of treatment to cases in which it may prevent functional loss of the eye. This would eliminate such self-limiting diseases as episcleritis and certain types of conjunctivitis. However, he makes a strong point in advising against this medication in all types of corneal involvment for prolonged periods of time. Curiously enough he fails to call attention to the potential danger of steroid treatment in fungus infections.

In his studies of the glycogen metabolism of the cornea, and the possibility of an inhibitory action by the steroids, he found to his surprise an increased glycogen content of the inflamed tissues. This may be either the result of leukocytic infiltration or of an actual glycogen formation in the stroma. In eyes treated with cortisone, a relative lack of glycogen could actually be demonstrated. This finding was not interpreted as a "glycogen stabilization" but as a decreased glycogen formation.

PAS stain showed no difference in the acid polysaccharide contents of control eyes and those treated with cortisone. However, the metachromatic changes found in control eyes could not be demonstrated in eyes treated with cortisone. A possible explanation of this finding is that cortisone causes a high degree of polymerization of the mucopolysaccharides.

The second main part of the volume is devoted to some highly interesting theoretical and experimental aspects of the effect of desoxycorticosterone on the eye. This agent may induce an acute inflammatory reaction in the eye which, however, does not necessarily resemble either a chronic or acute focal infection in the human eye. It remains

questionable whether or not it plays any part in endogenous inflammation of the human eye.

Although the major part of the monograph is devoted to experimental and theoretical features, it can be recommended highly to every clinician who is not satisfied with using these valuable adjuvants in our present-day therapy by trial and error only.

Stefan Van Wien.

ELECTROMYOGRAPHY IN NERVOUS DISEASES AND IN CRYPTOTETANY. By N. Rosselle, K. De Doncker, P. Jolie, A. Van Betsbrugge, and S. Ligot. Louvain, Belgium, E. Nauwelaerts, 1959. Price: paperbound, $5.00; clothbound, $6.00.

This paperbound monograph of 159 pages contains 180 figures illustrative of various electromyographic patterns. Thirty case examples of neuromuscular disease are presented, chiefly peripheral in origin. The authors state that it was not their intention to publish a detailed study of electromyography. They divided the work into two parts; the first one being a systematic explanation of electromyographic data, the second an atlas of clinical cases. The authors deliberately omitted a bibliography in this edition since standard reference works are readily available.

This small book can be read in less than an hour but it is questionable whether it would be worthwhile for the ophthalmologist to do so. The chief defect is the extremely poor English translation of the original text. The uninitiated may be hopelessly confused and to one moderately experienced in electrophysiology, the meaning of the authors is not always clear.

The theoretical treatment is extremely cursory and does not present anything like a comprehensive background for the subject of electromyography. In attempting to be terse, the authors have sacrificed much of the value of the atlas. The information presented is inadequate for a proper understanding by the newcomer and too elementary for the experienced electromyographer. The standard topical breakdown into neurogenic, myogenic, myasthenic, and myotonic disorders is presented along with a discussion of cryptotetany. The photographs are, however, quite good and reproduced on good quality paper.

This monograph would not be of particular help to the ophthalmologist interested in electromyography.

Goodwin M. Breinin.

GLAUKOM: EIN HANDBUCH. By Dr. Wolfgang Leydhecker. Berlin, Springer, 1960. 601 pages, 11 illustrations, references, index. Price: D.M. 89.60.

Professor Leydhecker, well known for his studies on glaucoma, and particularly for his investigations on provocative tests, is on the faculty at the University-Eye Clinic, Bonn, West Germany. His work is in the best traditions of the typical German "handbook" so familiar, and so valuable too, to us.

In his preface he points out that Schmidt-Rimpler reviewed the literature on glaucoma up to 1908, and Peters performed the same service in covering the literature from 1908-1930. Leydhecker takes us from 1930 to the present. He has done this very well, for it was a most arduous and time-consuming job because the literature on all phases of glaucoma is well-nigh overwhelming and widely scattered throughout the world.

His book is directed toward the clinical aspects of glaucoma and every aspect of the glaucomas from anatomy on through diagnosis and treatment. It forms a magnificent and accurate short encyclopedia for reference and bibliographic studies. In it you can be sure to find the latest information in this field.

Derrick Vail.

TRANSACTIONS OF THE PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY. 43rd annual meeting, Las Vegas, Nevada, 1959. 319 pages and index. Edited by Earle H. McBain.

As has been true in the past the 1959 *Transactions* of this very active West Coast specialty society contains a number of interesting and timely papers, presented at the meeting held in Las Vegas in May, 1959. Aside from papers on "Medicine in a changing world," "The psychology of radiation injury," "Genetics in medicine and public health," and "Cardiac arrest," all subjects of interest to all branches of medicine, there are 10 papers of purely ophthalmologic character.

Dr. S. S. Cullen presents a paper on "Anesthesia in ophthalmology," discussing the importance of maintaining an airway in even minor surgery, and other factors of importance in inducing and maintaining a safe anesthetic state. In an interesting study of "Ophthalmological problems of the American Indians," Thygeson and Dawson found trachoma to be still the most important problem although the program of detection and treatment now being carried out is beginning to have some effect. Phlyctenulosis is quite common, due to the high incidence of tuberculosis, but glaucoma, uveitis, herpetic keratitis, and ophthalmia neonatorum appear to be rare.

Pischel and Colyear summarize their first 100 cases in "Clinical results of light coagulation therapy." In retinal detachments they found the greatest value of the method as a prophylactic for holes in undetached retinas, for the treatment of tears when the retina settled completely, and as a postoperative adjunct when diathermic coagulation was inadequate. Success was also obtained in Von Hippel-Lindau disease, Eales' disease, Leber's miliary aneurysms, and in some cases of tumors.

William K. McEwen, in a discussion of "The vitreous: More to be pitied than censured," attempts to explain the structure of this substance, summarizing it as "dilute, slightly viscous solution of salts, plasma proteins, and hyaluronic acid contained in a fine meshwork of a collagen-type insoluble residual protein." Robert P. Burns reports three cases of "Mucormycosis of the sinuses, orbit, and central nervous system," a rare, highly fatal fungus infection occurring especially in patients with diabetes and blood dyscrasia.

Broadbent and Woolf discuss the "Physiological mechanisms in the success and failure of grafts and flaps about the orbit." Bailey and Swan describe their method of "Cinematography of the retinal venous pulsation," which has been beautifully demonstrated at several other meetings. In a paper on "Chymotrypsin in cataract surgery," Jensen, Lyda, and Hargiss discuss their results in 62 cases of cataract extraction with use of the enzyme and 47 in which it was not used, concluding that it is most useful in patients under 50 years of age, in high myopia, in intumescent or hypermature cataracts, and in those with a thin capsule.

Maumenee describes "Serous and hemorrhagic disciform detachment of the macula," terms which he prefers on histopathologic grounds to the more commonly used terms. The final ophthalmologic paper, by Lester Jones, deals with a new method for the surgical cure of entropion based on a resection of a tongue of conjunctival-fascial tissue at the base of the inferior tarsus.

William A. Mann.

ABSTRACT DEPARTMENT

EDITED BY DR. F. HERBERT HAESSLER

Abstracts are classified under the divisions listed below. It must be remembered that any given paper may belong to several divisions of ophthalmology, although here it is mentioned only in one. Not all of the headings will necessarily be found in any one issue of the Journal.

CLASSIFICATION

1. Anatomy, embryology, and comparative ophthalmology
2. General pathology, bacteriology, immunology
3. Vegetative physiology, biochemistry, pharmacology, toxicology
4. Physiologic optics, refraction, color vision
5. Diagnosis and therapy
6. Ocular motility
7. Conjunctiva, cornea, sclera
8. Uvea, sympathetic disease, aqueous
9. Glaucoma and ocular tension
10. Crystalline lens
11. Retina and vitreous
12. Optic nerve and chiasm
13. Neuro-ophthalmology
14. Eyeball, orbit, sinuses
15. Eyelids, lacrimal apparatus
16. Tumors
17. Injuries
18. Systemic disease and parasites
19. Congenital deformities, heredity
20. Hygiene, sociology, education, and history

12
OPTIC NERVE AND CHIASM

Chwirot, R. **Optic atrophy at the level of the disc after section of the nerve.** Ophthalmologica **138**:436-448, Dec., 1959.

With Arasimowicz the author has worked out a surgical approach to the retrobulbar portion of the optic nerve in the dog which is relatively atraumatic and affords good exposure of the nerve and its blood vessels. The retinal vessels in the dog are branches of the ciliary system and enter the nerve from below about 2 mm. behind the lamina cribrosa. Before entering the nerve or the globe the ciliary arteries course in a fatty sheath that can easily be stripped off the nerve. A fairly long posterior portion of the optic nerve has no such fatty sheath and no relations to any of the major orbital blood vessels. This setup permits clean sectioning of the optic nerve in a number of well-defined planes, with or without inclusion of the vessels in the fatty sheath.

The effects of sectioning of the optic nerve were observed ophthalmoscopically. Depending on whether or not the retinal vessels had been included in the sectioning, two types of optic atrophy could be distinguished: (1) an immediate and progressive form characterized, at first, by the signs of retinal ischemia and, later on, by sinking-in of the lamina cribrosa so that the final picture was a deeply excavated, hyperpigmented nerve head with hardly perceptible retinal vessels, and (2) a late form characterized by no ophthalmoscopic changes of any kind during the first few months and a slowly progressive primary optic atrophy thereafter. (9 figures, 10 references) Peter C. Kronfeld.

Sanna, M. **Vascular pseudopapillitis.** Riv. oto-neuro-oftal. **33**:471-484, July-Aug., 1958.

The author outlines his findings in nine patients who showed edema of the optic disc, a decrease in visual acuity, and field defects. The differences between optic neuritis and choked disc are then mentioned. The author feels that the term "vascular pseudopapillitis" can be applied to his cases since they are most likely the result of an occlusion of the vascular network of the optic nerve. (11 figures, 15 references) Wm. C. Caccamise.

Zamorani, G. **Changes in the visual**

field in various affections of the optic nerve following the injection of nicotinic acid into the optic foramen. Riv. oto-neuro-oftal. **33**:349-381, May-June, 1958.

The author evaluated the visual field changes that occurred in 29 patients (20 with chronic glaucoma, six with opticochiasmatic arachnoiditis, and three with partial optic nerve atrophy) after the injection of nicotinic acid into the area of the optic foramen. The author was greatly impressed with the apparent improvement in the visual field that occurred in the majority of the patients. He attributes this to an active hyperemia that follows such an injection. (2 figures, 29 field diagrams, 8 references)

Wm. C. Caccamise.

13
NEURO-OPHTHALMOLOGY

Alema, G., Vanni, V. and D'Orio, R. **The syndrome of Foster Kennedy on a vascular basis.** Riv. oto-neuro-oftal. **34**: 570-584, Sept.-Oct., 1959.

Four cases reported by the authors together with their review of the literature indicate that the Foster Kennedy syndrome can be of vascular origin in a significant number of cases. (5 figures, 14 references) Wm. C. Caccamise.

Boeri, R. **Ophthalmic hemicrania as a symptom of cerebral angioma.** Riv. oto-neuro-oftal. **34**:126-132, Jan.-Feb., 1959.

Periodic headache is one of the more frequent symptoms of cerebral angioma. The author presents two cases of cerebral angioma in which the only subjective manifestation was hemicrania together with disturbances in vision, that is, typical migraine. (2 figures, 9 references)

Wm. C. Caccamise.

Collier, M. **Myotonic dystrophy of Steinert.** Arch. d'opht. **19**:850-853, Dec., 1959.

The occasional neurologic complications of the myotonic dystrophy of Steinert include internal hydrocephalus, mesocephalic lesions, neuro-ophthalmologic involvements, Parkinson's disease, and flaccid paralyses. Psychic disorders are seen more commonly, however. The author reports a typical case of the disease in a woman aged 46 years with myotonic facies, ptosis, enophthalmos, atrophy of the muscles of mastication, laxity of the tempero-maxillary articulation, weakness of the musculature of the lips, convergent strabismus, and pseudohypertrophy of the right sternocleidomastoid muscle. Vision was reduced by cataract formation. Collier then studied the genealogy of the patient's family and found four involved subjects in two generations. All four were women but this is believed to be coincidental since previous studies have not shown a sex predominance. (5 figures) P. Thygeson.

Forlani, D. **A case of uveo-meningitis with optico-chiasmatic arachnoiditis.** Riv. oto-neuro-oftal. **34**:18-30, Jan.-Feb., 1959.

The author presents and discusses the clinical findings in a 30-year-old woman who developed the following symptoms successively: fever and fleeting joint pains, bilateral parotitis, bilateral granulomatous uveitis, bilateral optic neuritis, lymphocytic meningitis, bilateral dysacusia, paralysis of the right internal rectus muscle, convergence insufficiency, and neuro-ophthalmologic signs of an opticochiasmatic arachnoiditis. (3 figures, 27 references) Wm. C. Caccamise.

Frasca, G. **The hemorrhagic oculocerebral syndrome of Terson.** Riv. oto-neuro-oftal. **34**:544-558, Sept.-Oct., 1959.

The author discusses in a very informative manner a syndrome consisting of a vitreous hemorrhage and a spontaneous subarachnoid hemorrhage. This syndrome was first reported by Terson in 1926. A

study of the literature by the author revealed only 14 reported cases. A summary of each of these cases appears in this article by Frasca. The author then adds his own case in a 50-year-old man to this list. (3 figures, 32 references)

Wm. C. Caccamise.

Fregnan, E. **Progressive facial hemiatrophy and ocular lesions.** Riv. oto-neuro-oftal. **33**:636-661, Nov.-Dec., 1958.

The author reviews the literature pertaining to progressive facial hemiatrophy and the ocular manifestations that have been reported in association with this disease. Detailed case histories in two of the author's own patients, one a 10-year-old girl and the other a 50-year-old woman, are included in this enlightening paper. (8 figures, 1 table, 90 references)

Wm. C. Caccamise.

Laterza, A. and Tagliacozzo, R. **The associated movement of lowering of the upper lid with downward rotation of the eyeball.** Riv. oto-neuro-oftal. **34**:39-47, Jan.-Feb., 1959.

The authors present the case of a 52-year-old man in whom lowering of the upper lid on downward gaze persisted in the course of a remission of a vascular syndrome of the brain stem with facial paralysis. (13 references)

Wm. C. Caccamise.

Mironi, F. **The syndrome of Adie.** Riv. oto-neuro-oftal. **34**:585-589, Sept.-Oct., 1959.

The author points out that the syndrome of Adie has been well defined on a clinical level but that the physiopathologic interpretation is still uncertain. He presents his findings in a 13-year-old girl; he believes that the syndrome may have its pathogenesis in a mesencephalohypothalamic lesion. (15 references)

Wm. C. Caccamise.

Schulze, A. **Differential diagnosis of suprasellar tumors.** Klin. Monatsbl. f. Augenh. **136**:166-185, 1960.

Three groups of 21 cases of the most frequent suprasellar tumors, namely pituitary adenoma, craniopharyngioma, and meningioma of the tuberculum sellae, were compared and evaluated from the point of view of diagnosis and differential diagnosis. Subjective complaints, ophthalmologic, systemic, radiologic, and radiographic findings were considered in this study. The characteristic radiologic appearance of the sella in the different groups is demonstrated in figures and discussed in detail. Arteriography and pneumoencephalography are valuable diagnostic aids in cases in which the diagnosis is doubtful. (12 references, 7 figures, 8 tables)

Gunter K. von Noorden.

Vanni, V. and Alema, G. **Severe stellate neuroretinitis resulting from diffuse papilloretinal edema in a case of intracranial hypertension caused by a brain tumor.** Riv. oto-neuro-oftal. **33**:440-448, July-Aug., 1958.

The authors describe and discuss the findings in a 20-year-old woman who had diminished visual acuity and severe headache. Ophthalmoscopic examination revealed a very severe bilateral neuroretinitis with a star-shaped macular figure, cotton-wool exudates, retinal hemorrhages, and neuroretinal edema. It was initially felt that the eye findings were attributable to a focus of infection. However, electroencephalographic studies revealed a circumscribed focus in the left frontal region. Angiography showed a large avascular tumor which in histopathologic study proved to be an astrocytoma. The authors relate the fundus picture to protracted blood stasis that can result from slight intracranial hypertension. (1 figure, 37 references)

Wm. C. Caccamise.

Vanni, V., Vizioli, R. and Maccagnani, F. **An unusual case of photogenetic epilepsy.** Riv. oto-neuro-oftal. **34**:590-597, Sept.-Oct., 1959.

Photogenetic epilepsy is that type of epilepsy in which seizures are precipitated by exposure to light. Attacks were provoked by movies, television, and similar stimuli. The authors present in detail their findings in an 11-year-old girl. (2 figures, 19 references)

Wm. C. Caccamise.

14
EYEBALL, ORBIT, SINUSES

Dorello, U. **The eyes and the sinuses—the relationship between inflammatory processes of the orbit and those of the paraorbital sinus.** Riv. oto-neuro-oftal. **33**: 499-511, Sept.-Oct., 1958.

The author found disease of one or more of the sinuses in all but five of 40 patients with orbital inflammation. He feels that in all patients with orbital inflammation a thorough study of the sinuses should be carried out. (6 figures, 20 references) Wm. C. Caccamise.

Fregnan, E. and Crepalpi. A. **Solitary neurinoma of the orbit.** Riv. oto-neuro-oftal. **34**:48-71, Jan.-Feb., 1959.

The authors present the clinical and histopathologic findings in a nine-year-old girl with left exophthalmos. Microscopic study revealed a neurinoma. (6 figures, 46 references) Wm. C. Caccamise.

Golovine, S. **Tumors of the eye and orbit observed in Yemen.** Arch. d'opht. **19**:854-857, Dec., 1959.

The author notes the frequency of ocular and orbital tumors encountered in the hospital of Taiz and states that when seen they have often developed to a size not common in Europe and are inoperable. He gives case reports of representative tumors, including both benign and malignant types. (1 reference)

P. Thygeson.

Jochmus, H. **Piezometry in the diagnosis of exophthalmos.** Klin. Monatsbl. f. Augenh. **136**:196-203, 1960.

The compressibility of the orbital contents was determined in 50 healthy eyes, and in 53 patients with unilateral or bilateral exophthalmos. The measurements were carried out with the piezometer of Jaeger. In orbital tumors the compressibility is largely dependent on cellular type and seat of the lesion and was generally found to be more or less diminished. In inflammatory exophthalmos, however, the compressibility of the orbital contents was normal, or only slightly reduced. In endocrine exophthalmos, normal or increased compressibility was found, unless malignant exophthalmos was present in which case compressibility was reduced. While this method appears to be of doubtful prognostic value in endocrine exophthalmos, it is definitely useful in the differential diagnosis of orbital disease leading to proptosis. (5 figures, 1 table, 18 references)

Gunter K. von Noorden.

Hynes, Wilfred. **Treatment of contracted socket with a non-contractile lining with a note on eyelid reconstruction.** Brit. J. Plast. Surgery **12**:242-251; Oct., 1959.

To correct the absence or shallowness of the lower fornix when there is adequate conjunctiva in the socket, the author has devised a procedure which employs a pedicle of skin from the lower lid drawn through an incision made completely through the base of the lid. Across the middle of the socket from canthus to canthus an incision is made in the conjunctiva; above the incision the conjunctiva is undermined and slid upward, and

below the incision the conjunctiva is dissected free from Tenon's capsule and brought down to line and form the posterior surface of the lower lid. The incision through the orbicularis at the base of the lid extends across the whole lid at the level of the lower border of the future lower fornix. The pedicle flap of skin is drawn through this incision and is sutured to the conjunctival edge above the original conjunctival incision. The skin and conjunctiva are united below and a free skin graft is used to cover the denuded portion of the lower lid from which the pedicle flap was transferred.

To correct a loss of both fornices with retraction of the lids, the lower fornix is reconstructed as described above. The upper fornix is reconstructed at a second operation, similar in principle but different in that two vertical incisions are made at the edges of the upper lid to permit a skin flap to be introduced from the anterior surface to form part of the posterior surface of the upper lid without disturbance of the levator muscle.

To correct loss of both fornices with short rigid lids, as may result from a severe injury or chemical burn, restoration of part of the eyelid is necessary in addition to relining of the socket. For such cases additional eyelid skin and lining may be provided by means of a composite auricular graft comprising both layers of the pinna together with the auricular cartilage in between.

Alston Callahan.

Molnár, L. **Encephalocele in the posterior orbit.** Szemészet **97**:41-46, 1960.

Intradural prolapse of the brain through the optic foramen occurred in a patient. The underlying cause is, in the author's opinion, a developmental anomaly. If this is present, any unphysiologic load may result in herniation of brain tissue.

Gyula Lugossy.

15
EYELIDS, LACRIMAL APPARATUS

Betetto, G. **Plexiform neurofibroma of the lid with conjunctival involvement.** Riv. oto-neuro-oftal. **34**:201-223, March-April, 1959.

The author presents the clinical and histopathologic findings in a 33-year-old woman with an enlargement of the left upper lid, particularly in its outer two thirds. Microscopic study revealed a plexiform neurofibroma. (7 figures, 64 references)

Wm. C. Caccamise.

Doders, W. **Gangrenous zoster ophthalmicus with loss of globe.** Klin. Monatsbl. f. Augenh. **136**:230-233, 1960.

A 64-year-old male patient was admitted after extensive involvement of the first and second trigeminal branch with zoster had led to loss of both lids and the entire globe. Only remnants of scleral tissue and necrotic conjunctiva were present on admission. Conservative treatment resulted in epithelial lining of the orbit. However, the patient died later from Brill-Symmers disease.

Gunter K. von Noorden.

Fox, S. A. **Marginal (tarsal) ectropion.** A.M.A. Arch. Ophth. **63**:660-662, April, 1960.

Marginal ectropion is a clinical entity characterized by lower lid eversion in which the skin and muscle remain firm but the tarsoligamentous sling gives way. To repair this condition the lid is split centrally and two straps are fashioned, one of skin and muscle and the other of tarsus and conjunctiva. The tarsoconjunctival strap is drawn nasally and resected; the skin-muscle strap is drawn temporally and a portion of it is also resected. (5 figures, 3 references)

Edward U. Murphy.

Leabert, R. Fernandez. **Double eyelid operation in the Oriental in Hawaii.** Plast. and Reconst. Surg. **25**:257, March, 1960.

In this article an operation to construct an upper lid fold is described. In the Caucasian lid the levator muscle expansion is attached to the skin after passing through the orbital septum. The absence of the lid fold in the Oriental is attributed to increased subcutaneous fat and blind ending of the levator muscle without attachment to skin.

The author describes a simple technique for thin lids with a tendency to fold, and a radical technique for thick lids with no fold. For thin lids an incision is made in the area of the fold. A second incision is made 7 to 8 mm. above the first, and the intervening skin is excised. The lower incision is sutured to the levator expansion and the skin edges are closed.

In the radical procedure a wider ellipse of skin with the underlying strip of orbicularis muscle and orbital septum are excised. Pressure is exerted on the globe to cause herniation of supraorbital fat, which is then excised. The inferior edge of the levator expansion is sutured to the skin at the edge of the lower incision with three nylon sutures and the skin edges are then approximated.

Joseph Amdur.

Marino, A. **Involvement of the mastoid in a patient with inflammation of the lid.** Riv. oto-neuro-oftal. **33**:717-724, Nov.-Dec., 1958.

The author describes the clinical findings in a three-year-old child with inflammatory edema of the lids of the right eye. In spite of both local and systemic antibiotic therapy the inflammatory process progressed posteriorly to the mastoid region. An incision in the mastoid region revealed a large amount of pus but the bone itself was not involved. After the incision and drainage the patient responded favorably to antibiotic treatment. The patient was well and discharged 17 days after admission to the hospital. (3 figures) Wm. C. Caccamise.

Mishra, S. and Sharan, J. **Palpebral neurilemmoma.** Brit. J. Ophth. **44**:252, April, 1960.

A palpebral neurilemmoma of the right upper lide of an 18-year-old Hindu male is described. The lesion is solitary, localized and usually encapsulated; it seldom becomes malignant. Treatment is by excision. (1 figure) Irwin E. Gaynon.

Mustardé, J. C. **The treatment of ptosis and epicanthal folds.** Brit. J. Plast. Surgery. **12**:252-258, Oct., 1959.

The author recommends levator resection for ptosis even when there is a complete paralysis of this muscle. To correct ptosis from total paralysis of the third nerve and for most cases of acquired ptosis, he uses fascia lata slings inserted in the form of a W to connect the lid margin with the frontalis muscle.

For blepharophimosis the author has devised an ingenious and most useful method of creating rectangular skin flaps with their bases in the lids and extending medially so that the medial canthal angle may be advanced and tied to the periostium medially. A complete understanding of this procedure can be obtained by a study of the drawings which accompany this article. Alston Callahan.

Orban, T. and Eröss, S. **Anomaly of development and tumor formation of the eyelid.** Ophthalmologica **139**:99-105, Feb., 1960.

The authors describe a patient in whom the facial cleft not only was crooked but showed a fault in closure. The patient also had a harelip, a coloboma of the lid and a wart-like mass on the lower lid

which became malignant. An epithelioma developed over the outer angle of the eye at the temporal end of the crooked facial cleft. (3 figures, 3 references)

F. H. Haessler.

Vancea, P., Balan, N. and Vaighel, V. **Mixed tumor of the lacrimal gland.** Arch. d'opht. **19**:861-866, Dec., 1959.

The authors discuss the literature on mixed tumor of the lacrimal gland and conclude that it is still uncertain whether its origin is mesodermal or ectodermal but that a congenital origin is accepted. They report the case of a man of 36 years of age who developed an exophthalmos with reduced vision of his right eye, due to tumor of the lacrimal gland. The tumor was excised and was found to be surrounded by a dense vascularized capsule. Three photomicrographs illustrate the essential features of the tumor, which include a mucous-embryonic type of stroma with zones of hyaline and osseous degeneration. (3 figures, 7 references)

P. Thygeson.

16
TUMORS

Forlani, D. **Association of a neurinoma of the orbit with aneurysm of the anterior cerebral artery.** Riv. oto-neuro-oftal. **34**: 489-499. Sept.-Oct., 1959.

The author states that a neurinoma is a neoplasm of the peripheral nerves and that it occurs only rarely in the orbit. He reports the case of a 39-year-old woman with a right exophthalmos and a palpable mass in the floor of the orbit close to the inferior lateral angle. Carotid arteriography revealed a small aneurysm in the anterior cerebral artery. Histopathologic study of the orbital mass showed that it was an orbital neurinoma, most likely arising from a ciliary nerve. The author raises the question of a common developmental abnormality for both the neurinoma and the aneurysm. (8 figures, 37 references) Wm. C. Caccamise.

Stewart, D. S. **Progress of metastatic carcinoma of the choroid secondary to mammary neoplasm.** Brit. J. Ophth. **44**: 53-55, Jan. 1960.

A woman, 51 years of age, complained of sudden diminution of vision in one eye several months after being treated for primary mammary carcinoma. Examination revealed a gray elevation in the macular area which was watched for several months and refracted frequently. The eye became progressively more hyperopic until a gross secondary detachment ensued. Central vision remained fairly good until the detachment, when the eye was enucleated. (2 figures) Morris Kaplan.

17
INJURIES

Abrams, J. D. **Iris hole following concussion injury.** Brit. J. Ophth. **44**:50-51, Jan., 1960.

A nine-year-old boy was struck in the eye without penetration of the globe but with resultant anterior chamber hemorrhage which promptly cleared. A tear in the iris extended through both its layers. (1 figure) Morris Kaplan.

Benkoe, E. **Visual field changes associated with exposure to industrial noise.** Ophthalmologica **138**:449-456, Dec., 1959.

In industrial workers exposed to continuous strong noise the author observed a characteristic sequence of field changes, namely first concentric contraction for colors, followed by a constriction for white and colors in the upper nasal quadrant and terminating in concentric contraction for all targets. Visual acuity, eyegrounds, pupils and ocular motility remained normal. Dark adaptation tests were non-revealing. By reducing the exposure to noise, the field changes could be made to regress in some of the cases. (4 figures, 13 references)

Peter C. Kronfeld.

Gat, L. and Nagy, J. **Self-inflicted chemical kerato-conjunctivitis.** Ophthalmologica **138**:406-412, Dec., 1959.

By the repeated topical instillation of mortar particles into her own eyes, a 17-year-old girl produced and maintained a bilateral chronic ulcerative conjunctivitis with secondary corneal involvement similar to Leber's conjunctivitis petrificans. The motive of this persistent self-mutilation was not clearly determined. (3 figures, 11 references) Peter C. Kronfeld.

Leibiger, W. **Two cases of ocular injury caused by contusion with a cracking whiplash.** Klin. Monatsbl. f. Augenh. **136**: 233-236, 1960.

In one case the blunt nonperforating injury resulted in violent posttraumatic iridocyclitis, followed by panophthalmitis and subsequent loss of the globe. Another patient was observed in whom the same injury caused a tear in the lens capsule followed by development of a traumatic cataract. (9 references)

Gunter K. von Noorden.

Oaks, L. W., Dorman, E. and Petty, R. W. **Tear gas burns of the eye.** A.M.A. Arch. Ophth. **63**:698-706, April, 1960.

Two patients with serious ocular injury from tear gas burns are reported. The occasional carelessness of law enforcement officers employing these chemicals and their lack of understanding of the possible gravity of such injuries is deplored. (7 figures, 9 references)

Edward U. Murphy.

Pintucci, F. and Andreocci, M. **Experiences with mucosal transplant in caustic burns of the eye.** Arch. di ottal. **63**:485-500, Nov.-Dec., 1959.

Treatment of severe caustic burns of the eye may include paracentesis and anterior chamber irrigation, removal of burned conjunctiva and replacement with buccal mucosa, a conformer, incisions into chemotic areas, amniotic membrane, denuding of the cornea, lamellar keratoplasty, or finally, the use of a conjunctival flap. If the corneal sensitivity before treatment is defective, the prognosis is bad. Surgery should be done within 36 to 48 hours. A graft may be taken from the upper fornix of the other eye. The transplant should be sutured carefully, especially at the limbus. Eighty-two cases are reported. (2 figures, 43 references)

Paul W. Miles.

de Rosa, Carlo. **Destruction of the eye by a solution of chloride of zinc.** Rassegna ital. d'ottal **28**:280, July-Aug., 1959.

While engaged at his work as a mechanic a particle of zinc and a solution of zinc chloride flew into the left eye. In spite of prompt and thorough treatment destruction began at the corneal epithelium and spread to the parenchyma. Clouding of the aqueous and of the anterior layers of the lens, hypotony, staphyloma, and loss of the globe followed. The danger from zinc salts needs to be emphasized and adequate protective measures enforced. (9 figures)

E. M. Blake.

Wuest, F. C. **Bitemporal hemianopsia following a traumatic lesion of the optic chiasm.** A.M.A. Arch. Ophth. **63**:721-723, April, 1960.

After a head injury in an automobile accident this 20-year-old man was found to have a bitemporal hemianopsia. There was macular sparing on one side and macular splitting on the other. The pathophysiology is discussed. (1 figure, 1 table, 7 references) Edward U. Murphy.

18

SYSTEMIC DISEASE AND PARASITES

Angelone, L. **Left homonymous hemianopsia in patients operated upon for pulmonary abscess.** Riv. oto-neuro-oftal. **33**: 699-716, Nov.-Dec., 1958.

The author reviews the literature and presents two case histories. In both patients surgery was performed on the left

lung because of a pulmonary abscess. During the immediate postoperative period, a left homonymous hemianopsia became evident. The author suggests that an air embolus was the probable cause of the visual defect. (43 references)

Wm. C. Caccamise.

Fischer, F. **The young diabetic with and without retinopathy.** Ophthalmologica **139**:55-61, Jan., 1960.

The problems related to diabetes in people under 40 years of age are increasing in magnitude. Better metabolic control and better protection against infections keep more and more juvenile diabetics alive until marrying age so that hereditary transmission of diabetes is increasing. The young diabetic usually lives through all stages of diabetic angiopathy which the older or elderly diabetic may be spared by death from other diseases.

The author compares a series of 68 young diabetics who have retinopathy (series C) with 121 young diabetics without retinopathy (series S). Both series are broken down into four groups according to age (1 to 15, 16 to 19, 20 to 29, and 30 to 39 years). Series C is characterized by 1. a high incidence of kidney involvement. 2. a high incidence of vascular hypertension and 3. longer duration of the diabetes. In series S there were only a few cases of mild hypertension and transient albuminuria.

The author's conclusion: the young diabetic with retinopathy is seriously ill in many respects; the young diabetic without retinopathy may be compared to an as yet unwritten chapter of a story with an uncertain, but most probably sad ending. (14 references)

Peter C. Kronfeld.

Fisher, C. M. **Ocular palsy in temporal arteritis; neurologic manifestations of the arteritides other than temporal arteritis.** Minnesota Med. **42**:1617-1630, Nov., 1959.

The neurologic manifestations of periarteritis nodosa, granulomatous angiitis, and idiopathic arteritis of the aortic arch (Takayasu's disease) are reviewed and compared in this concluding portion of the author's discussion of temporal arteritis. (51 references)

Edward U. Murphy.

Gobbi, G., Gualdi, G. and Ascarie, E. **Hemophthalmos in the course of thrombocytopathia.** Rassegna ital. d'ottal. **28**:343-344, Sept.-Oct., 1959.

A 62-year-old man, whose past and present health were normal, noted a sudden loss of vision in the left eye while pedalling a bicycle. Examination revealed a few cells in the aqueous and a cloudy vitreous. The ophthalmoscope showed slight pressure at the point of crossing of retinal veins and arteries. Blood smears revealed aniso- and poikilocytosis. This disease resembles von Willibrand's pseudohemophilia. (4 figures) E. M. Blake.

Gyi, Ko. **Intra-ocular gnathostomiasis.** Brit. J. Ophth. **44**:42-45, Jan., 1960.

Human infestation with the nematode Gnasthostoma spinigerum is very rare and when it does occur is probably caused by the ingestion of raw fish which acts as an intermediate host in the parasite's life cycle. A 28-year-old boatman received a blow by a cable swung out of the muddy waters of the river harbor. There was a small laceration of the lower lid which healed uneventfully. A few days later the eye became blood-filled and blind; when the blood subsided sufficiently for examination a live worm, which was five millimeters in length, was seen in the anterior chamber. It was eventually removed and found to be this rare nematode. The eye healed well. (2 figures)

Morris Kaplan.

Klauder, J. V. **Interrelation of some cutaneous and ocular diseases.** A.M.A. Arch. Derm. **80**:515-528, Nov., 1959.

The association of ocular and dermatologic disease is reviewed and a series of the author's cases from the Wills Eye Hospital presented. The conditions discussed are blepharochalasis, sarcoid, erythema multiforme (Stevens-Johnson syndrome), pemphigus, chancre, lymphoma, and melanoma. The scanty information in the literature on the length of eyelashes motivated their measurement in 250 persons. A gradual decrease in length was noted with advancing age. In adolescence they averaged about 9 mm.; after 60 years of age, 4 or 5 mm. was common. (16 figures, 36 references)

Edward U. Murphy.

Kroll, A. G. **Eye lesions in the 1957 influenza pandemic.** Vestnik Oftal. **3**:34-39, May-June, 1959.

Transient symptoms consisting of pains in the eyes, frequently associated with ocular movement or palpation, occurred rather often. More specific ocular conditions were seen in 36 patients during the period from Sept., 1957 to Jan., 1958. They were first noted one to ten days after the onset of influenza. Ocular lesions were much less frequent in school children and younger patients with influenza than among older patients. Sixteen had superficial keratitis, one had a deep variety of keratitis and two had keratitis with hypopyon. Iridocyclitis occurred in 11 patients. Nine patients were seen with tenonitis, scleritis, optic neuritis, phlegmon of the orbit and acute conjunctivitis. Cortisone instillation proved effective in iridocyclitis, but less so in the dendriform type of keratitis. (1 table, 6 references) Victor Goodside.

Scorciarini-Coppola, A. **Supraclinoid aneurysm of the internal carotid artery with unusual symptoms.** Riv. oto-neuro-oftal. **34**:31-38, Jan.-Feb., 1959.

The author discusses the case of a 47-year-old woman in whom a definite preoperative diagnosis of supraclinoid aneurysm of the left internal carotid artery was made possible through angiography and pneumo-encephalography. The value of these procedures in making a diagnosis in certain ophthalmologic cases is emphasized. (3 figures, 16 references)

Wm. C. Caccamise.

Wasserman, Edward and Glass, W. I. **Stevens-Johnson syndrome.** A.M.A. Arch. Int. Med. **104**:787-792, Nov., 1959.

A severe case of erythema multiforme exudativum in a 35-year-old white woman is reported. Although there was severe corneal involvement with ulceration and pseudo-membrane formation, practically complete recovery followed with final vision of 20/25 in the right eye and 20/20 in the less severely involved left eye. A chloramphenicol-hydrocortisone preparation was used locally along with systemic penicillin and ACTH. The differential diagnosis of such a case must consider all conditions with bullous eruptions of the skin and mucous membranes such as drug sensitivity, human foot and mouth disease, and pemphigus vulgaris. This case is of particular interest because of its apparent association with an epidemic of Type A Asian influenza and the suggestion that a virus may be the etiological agent. (4 figures, 23 references)

Edward U. Murphy.

Murro, S. and Walker, C. **Ocular complications in sickle-cell hemoglobin disease.** Brit. J. Ophth. **44**:1-24, Jan., 1960.

The recent great increase in influx of Negro colonials into England has brought into prominence sickle-cell anemia which had hitherto been reported mainly in America and in the clinics of West Africa. The disease, sickle-cell hemoglobin C, is found exclusively in the Negro race and has been reported to exist in from less than 1 to 11 percent of members of that

race; there are estimated to be 10 to 20 thousand cases in America and 40 million cases in the 200 million Negroes of Africa. Although there are numerous variations of the disease, generally it is characterized by recurrent infarctive episodes which may occur at any location and which may vary from being symptomless to being fatal. These infarctions are caused by obstructions in the capillaries brought about by the inflexibility of the sickle-shaped red cells which cannot complete passage through the capillaries. The basic pathology of the disease is a variation in the electrophoretic motility of the hemoglobin which in turn may take several variations which accounts for the various forms of the disease.

In the eye there may be found a characteristic retinopathy which seems to be confined to the periphery and is composed of numerous hemorrhages, fibrotic patches, atrophic areas, thrombosed veins and exudative retinal detachments. The hemorrhages tend to be recurrent as in Eale's disease. Diamox therapy was of some benefit although treatment is generally unsatisfactory.

To the general literature are hereby added nine cases of this disease which are described in some detail and in all of which the typical eye pathology was present. (11 figures, 37 references)

Morris Kaplan.

Radnot, M. **The importance of the eye in the function of the organs of internal secretion.** Ann. d'ocul. **193**:298-308, April, 1960.

Since many physiologic functions show a 24-hour rhythm, the author feels that the eye which receives varying light stimuli is responsible for some of the changes. He shows curves which indicate that exposure of the eye to a 400 watt bulb will cause an eosinopenia. He also feels that the ill effect of darkness on glaucoma is not due simply to a dilation of the pupil but affects the "hypothalamic-pituitary" system. (7 figures, 31 references)

David Shoch.

19
CONGENITAL DEFORMITIES, HEREDITY

Bowers, Dorrance. **Marfan's syndrome and the Weill-Marchesani syndrome in the S. family.** Ann. Int. Med. **51**:1049-1070, Nov., 1959.

About 350 cases of Marfan's syndrome have been reported in the literature since the condition was recognized. The author has found 33 cases in seven generations of one family. Two of these cases resemble the Weill-Marchesani syndrome. In the 17 affected members who were known to have been examined, 94 percent had dislocated lenses, 94 percent were dolichocephalic, 70 percent had arachnodactyly, and 15 percent showed clinical evidence of aortic disease. The average lifespan of 16 deceased individuals was 45 years. In this family, Marfan's syndrome seems to be transmitted by a single pleiotropic abnormal gene which, when expressed, results in an abiotrophy of the cardiovascular system. (5 figures, 8 tables, 47 references)

Edward U. Murphy.

Cascio, G. and Grisanti, G. **Etiopathogenetic relationships between "ethmoidism" and strabismus.** Riv. oto-neuro-oftal. **33**:546-568, Sept.-Oct., 1958.

So-called "ethmoidism of Bertolotti" is characterized by hypertelorism, platyrrhinia, narrowing of the palpebral fissure with a tendency for an antimongoloid slanting, and strabismus. The author presents the findings in four children who had ocular abnormalities in association with cranio-facial malformations. (14 figures, 34 references)

Wm. C. Caccamise.

Forlani, D. **Mandibulo-facial dysostosis and facial lipoderma.** Rassegna ital. d'ottal. **28**:262-279, July-Aug., 1959.

Three examples of this disfiguring affliction are reported and illustrated with excellent photographs; the subjects were two, three and 11 years of age. There was no family history of the same or other congenital defects. In one of the three subjects there was a lipoma at the outer canthus and adherent to the conjunctiva. Malformation of the external ear and one skeletal deformity were present in one of the patients; another had a swelling over the ciliary border of the eyelid and a nasal deformity. The third patient had a muscle defect of the right eye and a lipoma in the left lower lid. (18 figures, references) E. M. Blake.

Gardiner, P. A. and James, G. **Association between maternal disease during pregnancy and myopia in the child.** Brit. J. Ophth. **44**:172-178, March, 1960.

In a survey in which 77 school children were examined, 42 were found to have congenital myopia measuring over −4D. All of these children came from mothers who had had some physical irregularity during pregnancy. There is probably a definite relationship between the two and the myopia is probably the result of a type of intrauterine malnutrition. In the charts there is no history given as to the date of appearance of the myopia which would mark it as congenital. Prematurity was no factor and neither was the size of the infant. It is stated that hereditary influence was of no importance and yet only 25 of the children were asked about their parents' eyes. It is the general opinion that congenital myopia does not progress as does acquired myopia and therefore its presence in infancy would indicate that the myopia existed at birth. The interesting statement is made that myopia is the commonest cause of blindness in middle age in England. (14 references) Morris Kaplan.

Gualdi, G. **The syndrome of Möebius.** Rassegna ital. d'ottal. **28**: July-Aug., 1959.

The author describes a typical example of Möebius syndrome, which is characterized by a paralysis of the external rectus muscle and an associated facial paralysis. This has been defined as a congenital defect of abduction. The unilateral type is the more common form. The patient was a six-year-old boy whose health and inheritance were normal. One relative suffered a left facial paralysis. The majority of writers consider the syndrome to be an expression of agenesis of the cranial nerves. (2 figures)

E. M. Blake.

Magnussen, K. **Hereditary isolated ocular albinism with nystagmus and pendular movement of the head in rabbits compared with corresponding anomalies in man.** Arch. f. Ophth. **161**:502-518, 1960.

A simply recessive mutation in the rabbit results in isolated ocular albinism which corresponds to a human ocular albinism which, however, is the result of gonosomal recessive inheritance. Both mutations bring about suppression of pigmentation and various grades of visual defect. Nystagmus which is constantly observed in human albinos also occurs in some of the rabbits. In some of the rabbits pendular movements of the head are noted when the animal sits quietly. The relationship to responsible genes is discussed. (6 figures, 31 references)

F. H. Haessler.

Vancea, M. P. and Tudor, E. **Embryopathy of rubeola.** Ophthalmologica **139**: 105-111, Feb., 1960.

The authors describe a child who had numerous congenital anomalies—microphthalmos, dermoid cyst at the limbus, trophic ulcer of the cornea, mental abnormality and developmental anomalies of the thorax and spinal column. The mother had had rubeola during the second month of pregnancy. (4 figures, 9 references)

F. H. Haessler.

20
HYGIENE, SOCIOLOGY, EDUCATION, AND HISTORY

Demato, F. J. **Incidence and causes of blindness in the Maltese Islands.** Brit. J. Ophth. **44**:164-171, March, 1960.

This study is based on examination of 638 blind persons which is considered to be the total blind population of the Maltese Islands and represents a rate of 199 per 100,000 persons. The criterion for blindness was corrected vision of less than 3/60. The ratio to population is about the same as prevails in Great Britain. About two thirds of these persons were totally blind and the remainder had some degree of vision. The incidence of blindness seemed to rise sharply after the age of 50, with most to be found in the 60 to 79 year age group. The greatest cause of blindness was found to be myopia and following that disease in this order were cataract, glaucoma, diabetes, and trachoma. These causes accounted for 80.6 percent of all cases. (2 references)

Morris Kaplan.

Dunnington, John H. **Address of the President, Interdependence.** Tr. Am. Acad. Ophth. **64**:7-10. Jan.-Feb., 1960.

In this presidential address, a plea is made for greater organized cooperation between clinicians and basic scientists. Examples of such cooperation are the Bio-Sciences Information Exchange, the elucidation by Terry et al. of retrolental fibroplasia, and the work of the Josiah K. Macy, Jr. Foundation. (4 references)

Harry Horwich.

Fuchs, A. **Distribution of trachoma and different trachoma types in the world. Chapter from "Geography of Ocular Diseases."** Klin. Monatsbl. f. Augenh. **136**: 255-263, 1960.

African negroes are less frequently affected with trachoma than semitic populations. Trachoma is less damaging in the Far East than in eastern parts of the Mediterranean area. Arlt's line is rare in China, however, flame-shaped scars radiating from the upper margin of the tarsus into the tarsal conjunctiva were frequently observed. These scars rarely lead to pronounced entropion. Ptosis of the upper lid due to infiltration of Müller's muscle and characteristic of trachoma patients in Egypt is almost non-existent in China. (6 figures, 26 references)

Gunter K. von Noorden.

Sgrosso, S. **Early history of the surgical treatment of detached retina.** Arch. di ottal. **63**:461-467, Nov.-Dec., 1959.

De Luca in 1874 anticipated some modern ideas in his treatment of detached retina. He did a sclerotomy near the most bullous part of the detachment, removed the subretinal fluid, and applied cauterization. He and others tried to produce a localized choroiditis by injection of iodine or other caustic. Paul W. Miles.

Theobald, G. W. **Women and medicine.** Tr. Am. Acad. Ophth. **64**:11-15. Jan.-Feb., 1960.

Women were the first practitioners of medicine. There are many records of female physicians of antiquity—in Egypt, Greece, Germany, Italy, and so on. Women couched cataracts in Elizabethan England. The oblique eye muscles were first described by a woman. In the latter half of the 19th century, five medical colleges for women were opened in the United States; and by the turn of the century many women had distinguished themselves as medical missionaries. (5 references) Harry Horwich.

NEWS ITEMS

EDITED BY DONALD J. LYLE, M.D.
411 Oak Street, Cincinnati 19, Ohio

News items should reach the editor by the 10th of the month. For adequate publicity, notice of postgraduate courses and meetings should be received three months in advance.

DEATHS

Dr. Herbert Hartman Glosser, Wellsville, New York, died March 11, 1960, aged 83 years.

Dr. George A. Leahey, Lowell, Massachusetts, died April 1, 1960, aged 90 years.

Dr. John Boyd McMurray, Washington, Pennsylvania, died February 18, 1960, aged 81 years.

Dr. Ellis H. Steffensen, Detroit, Michigan, died April 9, 1960, aged 47 years.

Dr. Charles Aaron Turtz, New York, New York, died February 12, 1960, aged 68 years.

Dr. Franklin Calton Smith, Charlotte, North Carolina, died February 25, 1960, aged 65 years.

ANNOUNCEMENTS

CORNEAL SURGERY

A concentrated course in corneal surgery of two and one-half days' duration will be given under the direction of Dr. A. Benedict Rizzuti at the Brooklyn Eye and Ear Hospital on Thursday, Friday and Saturday, December 8th, 9th and 10th instead of on November 17th, 18th and 19th as previously announced.

Present surgical concepts of keratectomies and keratoplasties will be stressed. Allied subjects such as beta radiation, contact lenses, operating room photography, instrumentation, and so forth will be discussed by staff members. Surgical procedures in the operating room will be demonstrated according to availabiilty of donor material. Participants will be offered an opportunity to apply surgical principles on animal eyes.

The course is limited to six ophthalmologists; tuition is $100.00

Address inquiries to Mr. Henry Williams, Superintendent, Brooklyn Eye and Ear Hospital, 29 Greene Avenue, Brooklyn 38, New York.

CONTACT-LENS COURSE

A three-day course for ophthalmologists in the fitting of contact lenses will be given by Baylor University College of Medicine, Texas Medical Center, Houston, Texas, on November 8th, 9th, and 10th. The course will include one day of lectures and two days of practical demonstration. The practical demonstration will consist of edging and beveling, examination, and actual fitting. Students will fit each other with contact lenses under the supervision of the instructors. In addition there will be observations of patients who have been fitted with contact lenses in keratoconus, aphakia, corneal transplants, aniridia; and an observation of the iris lens.

Inquiries should be addressed to Dr. Louis J. Girard, Division of Ophthalmology, Baylor University College of Medicine, Houston 25, Texas. Registration fee is $100.00

TORONTO REFRESHER COURSE

The Faculty of Medicine, University of Toronto, will hold a refresher course in eye surgery March 20 to 22, 1961. The instruction will consist of lectures, operative sessions and a special symposium on cataract surgery.

Dr. Robert N. Shaffer, University of California, San Francisco, and Mr. B. W. Rycroft, F.R.C.S., London, England, will be guest surgeons. The staff of the Department of Ophthalmology will contribute extensively.

The course will be limited to 50 members and is open to eye, ear, nose and throat specialists. Application should be made to the Director, Division of Postgraduate Medical Education, Faculty of Medicine, University of Toronto, Toronto 5, Canada, before January 31, 1961.

On March 18th there will be a Departmental Research meeting and Dr. H. M. Burian, University of Iowa, will be guest speaker. Members of the Eye Surgery Course are invited to attend.

MISCELLANEOUS

REQUEST FOR USED COPIES OF AJO

Dr. Ronnie Holland, Mission Hospital, Quetta, Pakistan, requests that readers who have finished with their copies of THE AMERICAN JOURNAL OF OPHTHALMOLOGY send them to the Mission Hospital. Working in an isolated community, Dr. Holland and his colleagues find it difficult to keep up with recent medical literature.

SOCIETIES

COLORADO OPHTHALMOLOGICAL SOCIETY

At a recent meeting, the Colorado Ophthalmological Society was honored to have as its guest lecturer, Dr. Charles L. Schepens, Boston. Dr. Schepens' lectures were on the subject, "Retinal detachment: Recent concepts of its causation and treatment."

PENNSYLVANIA-NEW JERSEY MEETING

At the recent joint meeting of the Pennsylvania Academy of Ophthalmology and Otolaryngology

and the New Jersey Academy of Ophthalmology and Otolaryngology in Atlantic City, the following ophthalmic program was presented:

Dr. Edward A. Atwood, Paterson, New Jersey, presided at the symposium on "Clinical methods of examination," at which Dr. Charles M. Reel, New Kensington, Pennsylvania, spoke on "Gonioscopy," Dr. Andrew DeRoetth, Jr., New York, "Tonography," Dr. Charles D. J. Regan, Boston, "Indirect ophthalmoscopy," Dr. Carteret Lawrence, Baltimore, "Biomicroscopy of the fundus."

Dr. John K. Covey, Bellefonte, Pennsylvania, presided over the symposium on "Current ocular therapy," and Dr. Irving H. Leopold was participating moderator. Speakers were Dr. Abraham Schlossman, New York, "Use of steroids"; Dr. Francis Furgiuele, Philadelphia, "Antibiotic therapy"; Dr. Leonard Apt, Philadelphia, "Drug therapy in pediatric patients."

In addition to the symposium and instruction courses, papers were presented by Dr. John H. Dunnington, New York, "Complications following lens extraction," and Dr. William L. Benedict, Rochester, Minnesota, "Medical arts, sciences and services."

Oxford Congress

Prof. Norman Ashton, London, presented the Doyne Memorial Lecture at the recent Oxford Ophthalmological Congress. The subject of his address was "The exit pathway of the aqueous." Other features of the program included a discussion on "Carotid insufficiency," with Mr. V. H. Smith, Manchester, Dr. John Marshall, London, Dr. J. W. D. Bull, London, Prof. C. G. Rob, London, and Mr. S. J. H. Miller, London, as openers.

Papers were presented by Mr. A. A. Douglas, Dundee, "The eyes and vision in cerebral palsy"; Dr. A. Stanworth, Manchester, "Prognosis in uveitis"; Mr. Barrie R. Jones, London, "The Surgical cure of obstruction in the common lacrimal canaliculus"; Mr. D. Stenhouse Stewart, Hull, "Regeneration of the crystalline lens."

Mr. A. G. Leigh, London, opened the second session with a paper on "Problems of keratoconus." Other speakers were Dr. S. M. Drance, Saskatoon, Canada, "The use of long-acting cholinesterase inhibitors in the management of chronic simple glaucoma"; Mr. Dermot Pierse, Croydon, "Cataract extraction with alpha chymotrypsin"; Prof G. I. Scott, Edinburgh, "Orbital cellulitis and cavernous sinus thrombosis"; Dr. J. Worst, Groningen, Holland, "The clinical uses of low-vacuum contact lenses"; Mr. Martin Walker, Birmingham, "The prognosis in glaucoma"; Mr. P. Graham, Manchester, "Some problems arising from a survey of corneal disease"; Mr. Patrick Joyce, Dublin, "Peripheral cataract extraction."

The final feature of the program was a discussion on "Recent trends in the treatment of detachment of the retina," with Mr. Lorimer Fison, London, Mr. F. D. McAuley, Dublin, and Prof. G. Meyer-Schwickerath, Essen, West Germany, as openers.

Personals

Miss Evelyn F. Ballou, MT (ASCP), who is the supervisor (chief technician) in the Ophthalmic Pathology Laboratory of the Armed Forces Institute of Pathology, was named "outstanding medical technologist of the year" and winner of the 1960 Corning Award at the 28th annual convention of the American Society of Medical Technologists at Atlantic City, New Jersey. Miss Ballou also serves as administrative assistant to Mr. L. P. Ambrogi, chief of all the Histopatholgy Laboratories of the Armed Forces Institute of Pathology.

It gives The Journal pleasure to announce that Dr. Marc Amsler, Zurich, has been elected to honorary fellowship in the Royal Society of Medicine, London.

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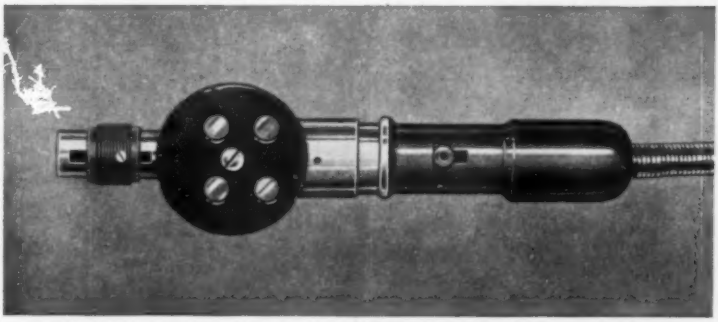

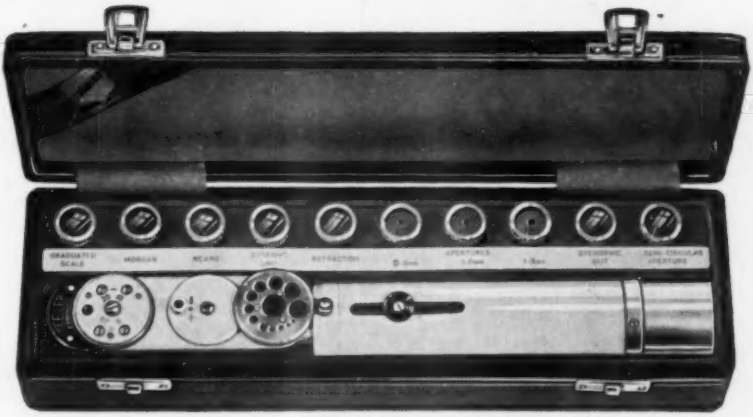

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